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PhD Thesis

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Assessment of neuromotor symptoms and adverse events in youth with psychosis: The Microsoft Kinect sensor and CYP2D6 genotyping

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Contents

Preface

In July 2010 I was offered the great opportunity to join the Research Unit at The Centre for Child and Adolescent Mental Health, Mental Health Services, Capital Region of Denmark, headed by professor, Anne Katrine Pagsberg. Recruitment of patients, assessments and data collection in the Tolerability and Efficacy of Antipsychotics (TEA) trial had just started one month earlier and I became one of the investigators of the research group. During the summer of 2011, a new idea arose: would it be possible to develop a quantitative instrument using the Microsoft Kinect Sensor as a supplement in the clinical assessment of neuromotor symptoms in adolescents with psychosis? Through a close and enriching interdisciplinary cooperation between the departments of Psychiatry (professor Anders Fink-Jensen), Child and Adolescent Psychiatry (professor Anne Katrine Pagsberg and myself), Neurology (doctor Kristian Winge) and Danish Technical University Compute (associate professor Rasmus Reinhold Paulsen and Jannik Boll Mathiassen) a new study exploring movements in patients with Parkinson's disease and young patients with first-episode psychosis using the Microsoft Kinect sensor was initiated. After a long period of protocol writing, application for funding and getting the relevant ethical and data storing approvals, recruitment of patients was initiated in February 2014. Data collection proceeded in both studies until August 2016. At that time, I had been enrolled as a PhD student for 3 years and started full time specialist medical training in Child and Adolescent Psychiatry in parallel with the writing of manuscripts and PhD thesis.

The present PhD thesis is based on the following manuscripts:

Rudå D, Einarsson G, Matthiassen JB, Correll CU, Jensen KG, Klauber DG, Richard CJ, Andersen ASS, Krøigaard S, Møllegaard Jepsen JR, Fagerlund B, Winge K, Clemmesen LKH, Pagsberg AK, Paulsen RR, Fink-Jensen A. *Measuring movements in adolescents with psychosis using the Microsoft Kinect sensor: a pilot study exploring a new tool for assessing aspects of antipsychotic-induced parkinsonism*. Child Adolesc Ment Health. 2020 May;25(2):79-94. doi: 10.1111/camh.12360. Epub 2020 Jan 7.

Rudå D, Einarsson G; Andersen ASS, Matthiassen JB, Correll CU, Winge K, Clemmesen LKH, Paulsen RR, Pagsberg AK, Fink-Jensen A. *Exploring Movement Impairments in Patients with Parkinson's disease using the Microsoft Kinect Sensor.* Submitted to the Frontiers in Behavioral Neuroscience.

Rudå D, Jensen KG, Decara MS, Fagerlund B, Møllegaard JR, Linnet K, Werge T, Correll CU, Fink-Jensen A, Jürgens G, Pagsberg AK. *CYP2D6 genotyping and antipsychotic-induced extrapyramidal side effects in a randomised trial of aripiprazole versus quetiapine extended release in children and adolescents, aged 12-17 years, with first-episode psychosis*. Submitted to the Journal of Clinical Psychopharmacology.

Related work:

Einarsson G. et al. (2018*) Computer Aided Identification of Motion Disturbances Related to Parkinson's Disease.* In: Rekik I., Unal G., Adeli E., Park S. (eds) PRedictive Intelligence in MEdicine. PRIME 2018. Lecture Notes in Computer Science, vol 11121. Springer, Cham. https://doi.org/10.1007/978-3-030-00320-3_1

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English summary

Background: Antipsychotic use in the pediatric population has been increasing over the past decades. Since the introduction of second-generation antipsychotics (SGA), concerns regarding side effects have shifted from extrapyramidal symptoms (EPS), which are prominent with first generation antipsychotics, to cardiometabolic side effects which constitute a major disadvantage with SGA. However, the risk of EPS in SGA is not negligible, neither in adults nor in children and adolescents. EPS are associated with low adherence to medication and low quality of life as well as high rates of remission of psychiatric symptoms, leading to rehospitalization.

EPS is a dose-dependent side effect and factors contributing to higher drug plasma concentration levels, such as genetic variations in drug-metabolizing enzymes, are likely to increase the risk of EPS development. Aripiprazole and quetiapine, two SGAs often used in youth, are both metabolized by hepatic cytochrome P450 enzymes, CYP2D6 and CYP3A4, which exert genetic polymorphism.

In daily clinical practice monitoring of EPS is done by clinical examination and use of clinical rating scales. Both methods are dependent on clinical experience and prone to inter-observer variability. In addition, the demand for physical contact of these methods can be experienced as unpleasant and even threatening by some patients with schizophrenia. To overcome these challenges, more objective methods to detect and quantify movement disorders are needed.

The objectives: To study whether genetically predicted CYP2D6 phenotype is associated with EPS in children and adolescents treated with aripiprazole or quetiapine in the Tolerability and Efficacy of Antipsychotics (TEA) trial. In addition, we wanted to develop and test a game-like instrument (*Motorgame*) using the Microsoft Kinect sensor to evaluate performance related bradykinesia, initially in a group of patients with idiopathic Parkinson's Disease and subsequently in a group of antipsychotic-treated young patients with psychosis.

Summary of Study I: The association between CYP2D6 genotype group, dose adjusted plasma concentrations of aripiprazole and quetiapine and extrapyramidal symptoms in a group of young patients with first-episode of psychosis was studied. At week 4 after treatment initiation, high proportions of akathisia were found in both treatment groups with no significant difference between study arms (47% in the aripiprazole group and 32% in the quetiapine-ER group; p=0.116), while the mean Barnes Akathisia Rating scale (BARS) score (±SD) was significantly higher in the aripiprazole-treated patients compared to quetiapine-ER-treated patients (1.45±1.19 versus 0.90±1.00; p=0.012). At week 12, the mean BARS score had significantly decreased (p=0.025) in the aripiprazole group, thus countervailing the difference between study arms. At week 4, significantly higher proportions of antipsychotic-induced parkinsonism were detected in the aripiprazole group (37%) versus the quetiapine-ER group (14%) (p=0.011). Correspondingly, a significantly higher mean Simpson Angus Scale (SAS) score (±SD) was found in the aripiprazole group (0.29±0.30 versus 0.17±0.25 in the quetiapine-ER group; p=0.023). The group difference in proportions and severity of parkinsonism was no longer seen at week 12.

In the aripiprazole group, CYP2D6 poor metabolizers (PMs) had a significantly higher dose adjusted plasma concentration than the extensive (normal) metabolizers (EMs) at week 4 (54.20±14.28 nmol/L/mg versus 33.11±13.71 nmol/L/mg; p=0.008) and borderline significantly higher dose adjusted plasma concentration at week 12 (49.40±24.61 nmol/L/mg versus 31.93±10.09 nmol/L/mg; p=0.054). No association between dose adjusted plasma concentration and CYP2D6 genotype groups was found in the quetiapine-ER group. No association between CYP2D6 genotypes and global BARS score or SAS scores was found in any of the study arms. No phenoconversion was detected, i.e. no difference between dose adjusted aripiprazole plasma concentration in patients without concomitant SSRI use compared to patients with concomitant SSRI (sertraline) use.

Summary of Study II: We developed and tested the *Motorgame* (a game-like application using the Microsoft Kinect sensor) in a group of patients with Parkinson's Disease (PD) (n=30) and healthy controls (n=33). In the group of patients, we found significant ($p<0.05$) associations between prolonged time of motor performance in the *Motorgame* and upper-body rigidity and bradykinesia (measured with Movement Disorder Society Unified Parkinson's Disease Rating Scale, section 3) with the strongest effects related to right hand movements ($p<0.001$). In the entire group of participants, prolonged time of motor performance in the *Motorgame* was related to higher rigidity SAS scores and Udvalget for Kliniske Undersøgelser (UKU) side effects rating scale hypokinesia scores ($0<0.05$). No significant association was found between time of motor performance in the *Motorgame* and motor speed (Token Motor Task; assessing fine motor skills), illness duration of PD or hours of daily physical activity. A significant ($p<0.001$) association between shortened time of performance in the *Motorgame* and higher scores on information processing (Symbol Coding Task) was found. A high level of participant acceptance of the *Motorgame* was observed.

Summary of Study III: The game-like instrument *Motorgame* was tested in a group of children and adolescents with first-episode of psychosis (n=21; 62% treated with antipsychotics and 38% antipsychotic-näive) and healthy controls (n=69). A significant association between prolonged time of motor performance in the *Motorgame* and higher SAS-scores for arm dropping (p=0.009) was found as well as a consistent practice effect for the *Motorgame* ($p<0.001$). No significant associations between performances on the *Motorgame* and age, height, body weight, gender, or information processing speed was detected. The *Motorgame* was well accepted.

Conclusion: The high incidences of akathisia and antipsychotic-induced parkinsonism in the group of children and adolescents with psychosis call for close monitoring to optimize treatment adherence and minimize motor side effects. The findings of this study indicate that akathisia and antipsychotic-induced parkinsonism seems to wear off over time. Our results do not support the use of routine CYP2D6 testing in the clinical setting. The *Motorgame* was able to detect upper-body rigidity and bradykinesia in patients with Parkinson's disease and healthy controls, as well as shoulder bradykinesia in young antipsychotic-treated patients with first-episode psychosis and healthy controls. The *Motorgame* was well accepted. Participants in both study groups found the game-like instrument fun and easy to use. However, further development of the instrument and larger scale studies are needed.

Dansk resumé

Baggrund: Forbruget af antipsykotisk medicin til børn og unge har været stigende i de sidste årtier. Siden introduktionen af 2. generations antipsykotika har fokus for bivirkninger flyttet sig fra ekstrapyramidale bivirkninger, som er hyppige ved brug af 1. generations antipsykotika, til kardio-metaboliske bivirkninger, som udgør den største ulempe ved brugen af 2. generations antipsykotika. Ekstrapyramidale bivirkninger ses dog stadig ved brug af 2. generations antipsykotika, både hos voksne samt børne- og unge patienter. Ekstrapyramidale bivirkninger er associeret med lav *compliance* til den medicinske behandling, lav livskvalitet, høj remissionsrate af psykiatriske symptomer samt hyppigere genindlæggelse.

Ekstrapyramidale bivirkninger er dosis-afhængige, og faktorer der bidrager til højere plasmakoncentrationer af antipsykotika, såsom genetiske variationer i de lægemiddel-metaboliserende enzymer, er sandsynligvis med til at øge risikoen for udvikling af ekstrapyramidale bivirkninger. Aripiprazol and quetiapin er to 2. generations antipsykotika som hyppigt anvendes til børn og unge. De metaboliseres begge af cytochrom P450-leverenzymerne CYP2D6 and CYP3A4, som udviser genetisk polymorfisme.

I daglig klinisk praksis vurderes ekstrapyramidale bivirkninger ved hjælp af klinisk undersøgelse og bivirkningsskalaer, som begge er kliniker-afhængige og dermed sårbare overfor inter-observatør variabilitet. Dertil kommer, at undersøgelsen kræver fysisk kontakt mellem patient og undersøger,

hvilket kan opleves som ubehageligt og ligefrem truende for nogle patienter med skizofreni. Der er derfor brug for mere objektive metoder til at opdage og kvantificere motoriske bivirkninger.

Formål: At undersøge hvorvidt den genetisk forventede CYP2D6 fænotype er associeret med forekomsten af ekstrapyramidale bivirkninger hos børn og unge i TEA projektet (the Tolerability and Efficacy of Antipsychotics trial). Desuden ønskede vi at udvikle og undersøge et spil-lignende instrument (*Motorgame*), som anvender Microsoft Kinect sensoren, til at evaluere bevægelsesrelateret bradykinesi, først i en gruppe af patienter med idiopatisk Parkinsons sygdom og dernæst i en gruppe antipsykotikabehandlede unge patienter med psykose.

Resumé af studie I: Associationen mellem CYP 2D6 genotypegruppe, dosisjusterede plasmakoncentrationer af hhv. aripiprazol og quetiapin samt ekstrapyramidale bivirkninger blev undersøgt i en gruppe unge patienter med førstegangspsykose. Vi fandt en høj forekomst af akatisi ved uge 4 uden forskel mellem de 2 behandlingsarme (47% i aripiprazol gruppen og 32% i quetiapin-ER (depot formulering) gruppen; p=0.116). Signifikant højere gennemsnit for global BARS score (±SD) blev fundet i uge 4 i de aripiprazolbehandede patienter (1.45±1.19) versus de quetiapin-ER-behandlede patienter (0.90±1.00; p=0.012). Ved uge 12 var gennemsnittet for global BARS scoren (±SD) faldet signifikant (p=0.025) i aripiprazolgruppen og forskellen mellem de to behandlingsarme havde udlignet sig. En signifikant højere incidens af antipsykotikainduceret parkinsonisme blev fundet i aripiprazolgruppen (37% versus 14% i quetiapine-ER-gruppen; p=0.011) i uge 4. Ligeledes fandt man et tilhørende signifikant højere gennemsnit for SAS score (±SD) i aripiprazolgruppen (0.29±0.30) versus quetiapine-ER gruppen (0.17±0.25; p=0.023) i uge 4. Disse forskelle sås ikke længere i uge 12.

I aripiprazolgruppen havde patienter med langsom CYP 2D6-metabolisering en signifikant højere dosisjusteret aripiprazol-plasmakoncentration sammenlignet med patienter med normal CYP2D6 metabolisering ved uge 4 (54.20±14.28 nmol/L/mg versus 33.11±13.71 nmol/L/mg; p=0.008) samt en borderline signifikant højere dosisjusteret aripiprazol-plasmakoncentration ved uge 12 (49.40±24.61 nmol/L/mg versus 31.93±10.09 nmol/L/mg; p=0.054). Der blev ikke fundet association mellem dosisjusteret plasmakoncentration og genotype-gruppe i quetiapine-ER-gruppen. Vi fandt ingen associationer mellem CYP2D6-genotyper og hhv. global BARS eller SAS-scorer i hverken aripiprazol- eller quetiapine-ER-gruppen. Der blev ikke fundet fænokonversion, dvs. ingen forskel mellem dosisjusteret aripiprazol-plasmakoncentration i gruppen af patienter

uden samtidig SSI-behandling sammenlignet med gruppen af patienter med samtidig SSRI-behandling.

Resumé af studie II: Vi udviklede og undersøgte *Motorgame* (en spil-lignende applikation, der anvender Microsoft Kinect sensor) på en gruppe patienter med Parkinsons Sygdom (n=30) og raske kontrolpersoner (n=33). I patientgruppen fandt vi signifikante ($p<0.05$) associationer mellem forlænget tid af den motoriske udførelse i *Motorgame* og hhv. øvre kropsrigiditet og bradykinesi (målt med Movement Disorder Society Unified Parkinson's Disease Rating Scale, sektion 3), med de stærkeste effekter relateret til bevægelser i høje hånd ($p<0.001$). I hele gruppen af forsøgsdeltagere var forlænget tid af den motoriske udførelse i *Motorgame* relateret til højere SAS-rigiditets-scorer og UKU-hypokinesi-scorer ($0<0.05$). Ingen signifikante associationer mellem tiden af den motoriske udførelse i *Motorgame* og motorisk hastighed (Token Motor Task, som måler finmotoriske evner), varighed af Parkinsons Sygdom eller antal timer daglig fysisk aktivitet blev fundet. En signifikant ($p<0.001$) association mellem forkortet tid af den motoriske udførelse i *Motorgame* og højere scorer i informationsbearbejdning (Symbol Coding Task) blev set. Vi fandt en høj grad af deltagertilfredshed med *Motorgame.*

Resumé af studie III: Det spil-lignende instrument *Motorgame* blev testet i en gruppe børne- og ungepatienter med førstegangspsykose (n=21) og raske kontrolpersoner (n=69). Vi fandt en signifikant sammenhæng mellem forlænget tid af den motoriske udførelse i *Motorgame* og højere SAS-scorer for *arm dropping* ($p=0.009$) sammen med en konsistent retest-effekt for *Motorgame* ($p<0.001$). Der var ingen signifikant association mellem motorisk udførelse i *Motorgame* og hhv. alder, højde, kropsvægt, køn og informationsbearbejdning. *Motorgame* var acceptabelt for deltagerne og blev vurderet som nemt og sjovt at bruge.

Konklusion: Den høje forekomst af akatisi og antipsykotikainduceret parkinsonisme hos børn og unge med psykose peger på et tydeligt behov for tæt monitorering med henblik på at optimere *compliance* i forhold til den medicinske behandling og minimere de motoriske bivirkninger. Resultaterne fra dette studie tyder på, at akatisi og antipsykotikainduceret parkinsonisme er bivirkninger som aftager over tid. Vores resultater understøtter ikke, at CYP2D6 testning anvendes rutinemæssigt i den kliniske hverdag.

Motorgame var i stand til at opfange øvre kropsrigiditet og bradykinesi hos patienter med Parkinsons sygdom og deres raske kontroller samt skulder-bradykinesi hos unge antipsykotikabehandlede patienter med førstegangspsykose og deres raske kontroller. Det spil-

lignende instrument fik gode vurderinger af begge studiegrupper. Der er behov for en videreudvikling af instrumentet samt flere og større studier.

List of abbreviations

AIMS = Abnormal Involuntary Movement Scale

AIP = antipsychotic-induced parkinsonism

AOS = adult onset schizophrenia

BARS = Barnes Akathisia Rating Scale

CAMHS = Child and Adolescent Mental Health, Mental Health Services

CI = confidence interval

CYP = Cytochrome P450

DDPA = Danish Data Protection Agency

ECG = Electrocardiography

EM = extensive (normal) metabolizer

EOS = early onset schizophrenia

EPS = extrapyramidal symptoms

ER = extended release

EUFEST = European First-Episode Schizophrenia Trial

FGA = first generation antipsychotics

GABA = gamma-aminobutyric acid

GAPD = Global Assessment of Psychosocial Disability

ICD = International Classification of Diseases and Related Health Problems

IM = intermediate metabolizer

IQR = interquartile range

ITT = Intention-To-Treat

L-dopa = L-3,4-dihydroxyphenylalanine

MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale

OR = odds ratio

PANSS = Positive and Negative Syndrome Scale

PD = Parkinson's Disease

PM = poor metabolizer

SAS = Simpson Angus Scale

SD = standard deviation

SGA = second generation antipsychotics

SPSS = Statistical Package for the Social Sciences

TD = tardive dyskinesia

TEA = Tolerability and Efficacy of Antipsychotics trial

UKU = Udvalg for Kliniske Undersøgelser

UM = ultra-rapid metabolizer

Background

Schizophrenia

Schizophrenia is a predominantly chronic neurodevelopmental disease characterized by a) positive symptoms, e.g. delusions, hallucinations, disordered thoughts and speech, and/or disorganized behavior, b) negative symptoms, e.g. social withdrawal, impaired motivation, and reduction in spontaneous speech and c) cognitive impairments, e.g. reduced working memory, impaired executive functions, reduced speed of information processing, impaired verbal and visual learning.[1] The disorder generally leads to impaired social and occupational functioning.[2] The median global incidence of schizophrenia is 15.2 per 100,000 individuals with prominent regional variation. Median point prevalence rate is 4.6 per 1,000 individuals. Epidemiological studies have described an overweight of males with a male:female ratio of 1.4:1[3]. However, this gender difference is not reflected in the prevalence rates which show an equal gender distribution.[3;4;5]

Early onset schizophrenia

Schizophrenia usually becomes manifest in early adulthood, but in approximately one fourth of the patients, symptoms occur already during childhood and the adolescent years.[6;7] Early onset schizophrenia (EOS) is per definition diagnosed before the age of 18 years and presents with an almost equal gender distribution.[8] Substantively worse prognosis and illness outcomes in EOS compared to adult-onset schizophrenia (AOS) have been found in several studies.[9-12] Clinical and neurobiological studies suggest that the same pathophysiology is involved in EOS and AOS[13;14].

Risk and etiologic factors are the same, but EOS is associated with more early language and motor problems.[11;14;15]

Motor disturbances

Movement disorders in schizophrenia

Several types of movement disorders are seen in patients with schizophrenia, some of which can be part of the pathology of schizophrenia (stupor, negativism, posturing, rigidity and other catatonic features)[16], while others are induced by antipsychotic medications due to their blockage of postsynaptic dopamine D2-receptors in the striatum producing extrapyramidal symptoms (EPS).

Extrapyramidal symptoms

Antipsychotic-induced EPS can be divided into acute and late-onset motor symptoms. Acute EPS develop within hours or days after initiation of antipsychotic treatment (or after dose increase) and include dystonia, akathisia and antipsychotic-induced parkinsonism (AIP).[17;18] Late-onset EPS usually develop after prolonged (several months to years) treatment and include tardive dystonia and tardive dyskinesia.

Dystonia is characterized by abnormal posture due to sustained muscle contraction, often focal, affecting muscles of the head, neck, back and extremities (with a lethal risk if the larynx or pharynx muscles are involved). Antipsychotic induced dystonia responds effectively to anticholinergic drugs such as biperiden.[19] Patients describe this motor symptom as extremely uncomfortable.[20] Acute dystonia can emerge into an irreversible tardive version. [20] Risk factors of dystonia are young age, male gender, substance abuse, and a family history of dystonia.[18;21]

Akathisia is characterized by both subjective inner restlessness and objective motor restlessness (pacing, rocking, unable to keep still). This motor symptom is experienced as highly disturbing by patients. Akathisia is not reversed by anticholinergic medications, but antipsychotic dose reduction, beta adrenergic blockers, and benzodiazepines have shown effect. [22]

Like idiopathic Parkinson's Disease (PD), AIP manifests with the triad of bradykinesia, skeletal muscle rigidity, and tremor. Risk factors of AIP are older age, female gender, cognitive deficits, and the presence of other acute EPS.[23] Antipsychotic-induced parkinsonism is a reversible condition, and dose reduction, switching to another antipsychotic drug or adding an anticholinergic drug is recommended.

Tardive dyskinesia (TD) is characterized by involuntary, repetitive facial movements such as grimacing, tongue protruding, and lips puckering, as well as torso and limb movements. The symptoms are, in contrast to idiopathic Parkinson' disease, not associated whit loss of dopaminergic neurons in substantia nigra. Unlike acute EPS, tardive dyskinesia is experienced as less disturbing by the patients and is usually first detected by family members or clinicians. Risk factors of tardive dyskinesia are older age, female gender, diabetes mellitus, alcohol abuse, organic brain damage, presence of negative symptoms of schizophrenia and history of acute EPS.[24;25] There is no evidence based treatment for TD. It is not recommended to attempt treatment of these motor symptoms with anticholinergic drugs, which in fact must be reduced if already in use.[20] The primary step is lowering the dose of the antipsychotic agent or switching to a SGA with a lower risk of EPS, followed by additional pharmacological treatment e. g. cholinesterase inhibitors, benzodiazepines or amantadine.

Risk of extrapyramidal symptoms in adults

The primary goal of antipsychotic treatment of schizophrenia is to reduce psychotic symptoms. The treatment management aims at optimizing treatment response and maintaining compliance while minimizing adverse effects. Studies in adults with schizophrenia have shown that the presence of EPS is strongly correlated with non-compliance[26;27], relapse, rehospitalisation[27;28] and poor quality of life.[29] Furthermore, TD is, due to obvious motor disturbances, often associated with social stigmatization.[30] Moreover, acute EPS increase the risk for later development of TD.[24;31] Epidemiological studies have found that nearly 60% of the patients treated with first-generation antipsychotics (FGA) develop EPS and 25-30% may develop irreversible TD.[32] SGA, which are more often used in clinical practice today, have a reduced risk of EPS compared to FGA, e.g. haloperidol,[33] but are more often associated with cardiometabolic side effects such as weight gain, elevated lipid, glucose and prolactin levels, and development of metabolic syndrome.[34-36]

In the EUFEST (European First-Episode Schizophrenia Trial) comparing the effects of five antipsychotic drugs (haloperidol, amisulpride, olanzapine, quetiapine and ziprasidone) over a year, EPS rates were 34% in the FGA group and 28% in SGA group. [37] Comparative meta-analyses show the highest incidence rates of EPS associated with the use of haloperidol, moderate rates with the use of risperidone, paliperidone, lurasidone and chlorpromazine, while lower rates of EPS with the use of asenapine, ziprasidone, amisulpride, iloperidone and aripiprazole. The lowest rates are seen

with the use of quetiapine, olanzapine, sertindole and clozapine[38-40]. Thus, significant differences in EPS profile are seen within the SGA group. Besides type of SGA agent, risk factors for development of EPS include increasing antipsychotic drug dose, history of previous EPS, and individual vulnerability to EPS.[41;42;42]

Risk of extrapyramidal symptoms in children and adolescents

Children and adolescents are more vulnerable to the development of EPS compared to adults.[43;44] A meta-analysis of the effects of aripiprazole in children and adolescents found a mean EPS incidence of 17.1 %.[45] Likewise, a Bayesian meta-analysis of SGAs showed significantly increased odds ratios (OR) (95% confidence interval (CI)) for EPS for all of the investigated drugs when compared with placebo: ziprasidone 20.56 (3.53-68.94), olanzapine 6.36 (2.43-13.84), aripiprazole 3.79 (2.17-6.17) and risperidone 3.71 (2.18-6.02), but not for quetiapine 2.54 (0.88-6.07).[44] In a naturalistic cohort study of pediatric patients (n=342) treated with quetiapine, olanzapine, risperidone, ziprasidone and aripiprazole and followed for up to 3 months, the incidence of drug-related parkinsonism was 15.2%, with the highest rate in the aripiprazole group (27.2%) and lowest in the quetiapine group (1.5%).[46] In a recent systematic review and network meta-analysis of 12 trials of antipsychotic treatment (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) in children and adolescents with schizophrenia-spectrum disorder, Pagsberg and colleagues found that molindone had more EPS (including akathisia) than aripiprazole, asenapine, olanzapine, quetiapine, risperidone and ziprasidone. All antipsychotics, except from asenapine, quetiapine and olanzapine, had more EPS than placebo. In addition, all antipsychotics, except from asenapine, quetiapine and ziprasidone, had more akathisia than placebo.[47] In another recent network meta-analysis of 20 trials of antipsychotic treatment (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, ziprasidone, clozapine, lurasidone, fluphenazine, haloperidol, loxapine, and thioridazine) in children and adolescents with schizophrenia, Krause and colleagues found only two significant effects regarding the use of antiparkinsonian medication in the pairwise meta-analysis and the network-meta-analysis, respectively, for paliperidone compared to placebo (OR 3.39 and OR 3.39) and for aripiprazole compared to quetiapine (OR 1.20 and OR 1.40). In the pairwise meta-analysis of the included placebo controlled studies (n=5), significantly more EPS were found for haloperidol, loxapine, risperidone and quetiapine).[48] In contrast, a recent

systematic review comparing results from 95 trials and 40 observational studies of FGA and SGA in children and young adults by Pillay and colleagues concluded that SGA may have a lower risk of any EPS and that high versus low dose of aripiprazole had little or no difference for any EPS compared to FGA. [49] Additionally, when SGA were compared to placebo, some degree of harm was found in relation to EPS, but little or no difference in risk for akathisia. [49]

Based on the current evidence, monitoring of EPS in youth patients treated with SGA is still of pivotal importance.

Antipsychotics

Historical view

In 1951 the newly synthesized antihistamine chlorpromazine was used by a French Navy anesthesiologist Henri Laborit as an agent to potentiate perioperative management and anesthesia of surgical patients. He observed that the chlorpromazine-medicated patients did not lose their consciousness during anesthesia, but became sleepy and showed a lack of interest.[50] Laborit shared these results with his colleague, psychiatrist Pierre Hamon at the Central Military Hospital in Paris. Hamon administered chlorpromazine (together with barbiturates and sedatives) to a patient suffering from mania with a subsequent reduction of psychiatric symptoms. [51] At the same time (1952) psychiatrists at the psychiatric clinic of Sainte-Anne Hospital in Paris, Jean Delay and Pierre Deniker, studied chlorpromazine in a large number of patients (n=300), also showing reduction of psychotic symptoms. [52] Chlorpromazine became the most prescribed antipsychotic drug through the 1960s and early 1970s and several new antipsychotic agents with same efficacy but different side effect profiles were introduced.[53]

In the early 1960s a group of German psychiatrists at Wander Pharmaceuticals in Bern, Switzerland, introduced clozapine, a new antipsychotic drug with minimal level of EPS, thereby introducing an 'atypical' (second generation) antipsychotic agent.[54] But clozapine was only on the market for a short period before being withdrawn due to reports of life-threatening incidents of agranulocytosis.[55] The later results of a double-blind study of clozapine in a treatment-resistant group of patients with careful monitoring of blood cell counts led to the reintroduction of the drug in 1990. [56]

In the early 2000s aripiprazole, an antipsychotic with D2-receptor partial agonist mode of action, was developed. Due to the D2 receptor functional selectivity of aripiprazole, some authors have

argued for a third-generation antipsychotic classification. [57] Since then, other antipsychotic drugs with partial agonism at the D2-receptor have been introduced, including cariprazine and brexpiprazole.

Antipsychotic mechanism of action

The most well-established target for all antipsychotic drugs is their antagonistic effect on the postsynaptic dopamine (D2) receptor in the dopaminergic pathways of the brain.[58]

FGAs have a high affinity (bind more tightly) to this receptor compared to dopamine and produce their antipsychotic effect at 60–80% of receptor occupancy in the basal ganglia of the forebrain.[59] Shortly after the introduction of chlorpromazine, a clear association of clinical response and EPS was seen. [60] More recent Positron Emission Tomography studies have shown that acute EPS emerge at 75–80% of D2 occupancy[61].

In general, SGAs are characterized by a broad receptor binding profile to several different serotonin, dopamine, muscarinic, adrenergic and histamine receptors. Many SGAs such as quetiapine, remoxipride, clozapine, olanzapine, sertindole, ziprasidone and amisulpride bind more loosely to the dopamine D2 receptor and dissociate rapidly from the D2 receptor (compared to dopamine)[62] In addition, they exert a relatively potent blockade of 5-HT_{2A} receptors[63] (with amisulpride as an exception). Kapur and Seeman have argued that the effect of SGAs is fully explained by these pharmacokinetic proporties[64] and state that the blockade of the 5-HT_{2A} receptor or other receptor systems 'may neither be necessary nor sufficient to achieve an antipsychotic effect'. [64] In contrast, Meltzer and colleagues have argued that the effect of SGA can be explained by a weak striatal D_2 receptor antagonism in combination with 5-HT2A receptor antagonism.[65] 5-HT2A receptors are located on cortical pyramidal and hippocampal cells, as well as on gamma-aminobutyric acid (GABA) neurons (a strong inhibitory neurotransmitter in the central nervous system).[66]

Under normal conditions, a stimulation of the D2 receptors in the basal ganglia acts as an inhibitor of the neuronal GABAergic inhibitory action on thalamus, leading to a facilitation of intended movement. As a consequence, the antagonistic effect of SGA on the D2 receptor in this area leads to a disinhibition of the inhibitory effect on GABAergic inhibitory action on thalamus, leading to a decreased facilitation of intended movement and subsequent EPS.[66]

5-HT2A receptors located on dopaminergic neurons in the ventral tegmental area and in substantia nigra interact with dopaminergic neurons in striatum, nucleus accumbens and the medial prefrontal cortex. Serotonergic activity in these areas has an inhibitory effect on dopaminergic activity. [67] Therefore, a blockade of serotonin receptors 5-HT2A indirectly increase the dopamine activity in the basal ganglia[68]. In conclusion, a high affinity to the 5-HT2A receptor together with a low affinity to the D2 receptor (driven by a fast dissociation from the receptor[64]) are thought to be responsible for the lower propensity of EPS seen in several SGAs compared to FGAs[69].

Aripiprazole

Aripiprazole is a quinolinone derivative with a very high affinity to the dopamine D2 receptor.[70;71] It acts as a partial agonist[72] at D2 and 5-HT1A serotonin receptors and as a antagonist at 5-HT2A receptors.[73] A partial agonist has a lower intrinsic activity at the D2 receptor than a full agonist. Consequently, aripiprazole acts as a functional agonist or as a functional antagonist, depending on the surrounding levels of dopamine. Therefore, aripiprazole is believed to function as an antagonist to the D2 receptor in the mesolimbic dopamine pathway, where high dopamine activity is thought to induce positive symptoms in patients with schizophrenia. In addition, aripiprazole will function as an agonist to D2 receptors in the mesocortical pathway, where low dopamine activity is believed to cause negative and cognitive impairment in schizophrenia. Furthermore, the blockade of the D2 receptors in the nigrostrial and tuberoinfundibular pathways, associated with development of EPS and elevated prolactin, respectively, is not believed to be as complete with aripiprazole as with typical dopamine D2 antagonists.[67]

Aripiprazole is well absorbed with peak plasma concentrations within 3-5 hours of administration and steady-state plasma concentrations by day 14.[74] Metabolization and elimination of the drug takes place in the liver via Cytochrome P450 CYP3A4 and CYP2D6 enzyme systems. The elimination half-life is about 75 hours for aripiprazole and 94 hours for its active metabolite dehydro-aripiprazole.[75]

Quetiapine

Quetiapine is a dibenzothiazepine derivative with low affinity for D2 receptor (antagonist) and relative higher affinity for 5HT2A receptor (antagonist) compared to most FGAs.[76] Quetiapine is

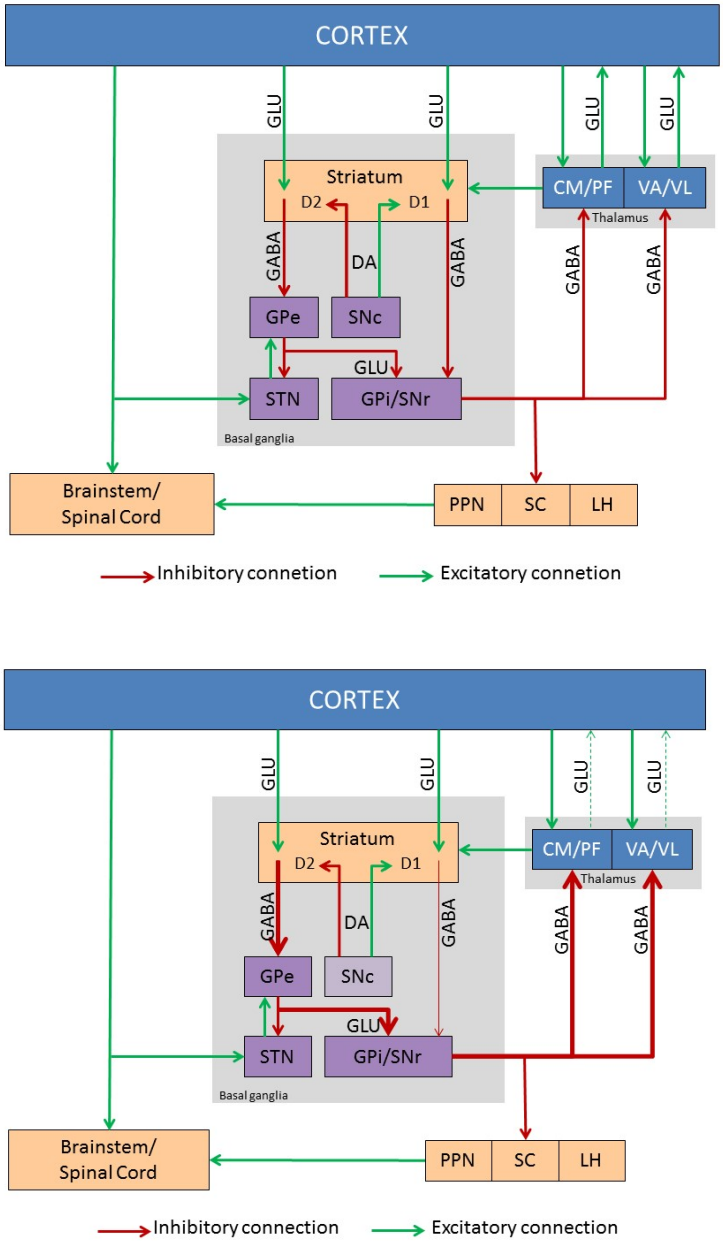
rapidly absorbed with peak plasma concentrations within 1-1.5 hours of administration.[77] Quetiapine is predominantly metabolized by CYP3A4 and to a lesser extent CYP2D6. [78;79] In this process 11 metabolites are formed, of which only two metabolites, 7-hydroxy-QTP and 7-hydroxy-N-desalkyl-QTP (norquetiapine), are pharmacologically active. The elimination half-life is 6-7 hours for quetiapine and 12 hours for norquetiapine. [80] The pharmacokinetic profile of quetiapine extended release (-ER) does not differ from the pharmacokinectic profile of quetiapine immediate release once absorbed and distributed. [77] Steady-state plasma concentrations are reached within 4 days for both formulations.[81]

Parkinson's Disease

The neuropathology of PD is characterized by degeneration of dopamine neurons in the substantia nigra and development of Lewy bodies (abnormal deposits of the protein alpha-synuclein) in the residual dopaminergic neurons.[82]

The substantia nigra pars compacta is important to the balance of the direct and indirect pathways of the basal ganglia (pathways responsible for the facilitation of intended movement). In healthy individuals, the substantia nigra exerts an activation of the direct pathway (See Figure 1) and an inhibition of the indirect pathway through the release of dopamine. In PD patients, the dopamine loss leads to diminished excitation (via D1 receptors) of the striatal neurons in the direct pathway and diminished inhibition (via D2 receptors) in the indirect pathway, causing increased inhibition of the thalamus, resulting in a net overactivity of the indirect pathway with less facilitation and more inhibition of movement[83]. This results in the appearance of PD core symptoms: Bradykinesia, rigidity, and resting tremor. As the disease progresses, postural instability often develops as a fourth cardinal symptom.[84]

Figure 1 Indirect and direct pathways of the basal ganglia in a non-affected person (upper picture) and a patient with Parkinson's Disease (lower picture).[85]



Abbreviations: CM centromedial nucleus of thalamus, D1 dopamine D1-type receptors, D2 dopamine D2-type receptors, DA dopamine, GABA gamma-aminobutyric acid, GLU glutamate, GPe globus pallidus external segment, GPi globus pallidus internal segment, LH lateral habenula, PF parafascicular nucleus of thalamus, PPN pedunculopontine nucleus, SC superior colliculus, SNc substantia nigra pars compacta, SNr substantia nigra pars reticularis, STN suprathalamic nucleus, VA ventral anterior nucleus of thalamus, VL ventral lateral nucleus of thalamus.

PD has rising global prevalence rates with age, estimated to be 0.4% in people aged 60 to 69 years, 1.1% in people aged 70 to 79 years and 1.9% in people over 80 years of age.[86]

Antipsychotic-induced parkinsonism

When blocking the D2-receptor in striatum by antipsychotics (D2-antagonists or partial D2 agonists), symptoms like those observed in idiopathic PD can occur. Antipsychotic-induced parkinsonism is characterized by symmetric bradykinesia, rigidity and tremor, which reverse upon antipsychotic discontinuation, switching to a lower-risk agent or by adding an anticholinergic drug.[87] Parkinsonian side effects to antipsychotics will often disappear within days or weeks, but may last for several months.[88;89]

Measuring motor disturbances

Clinical rating scales of movement disorders in psychiatry

In clinical practice, antipsychotic-induced movement disorders are usually assessed by clinical evaluation. However, a large number of rating scales for the evaluation of motor side effects exist, including the Abnormal Involuntary Movement Scale (AIMS)[90], Simpson-Angus Scale (SAS)[91] and the Barnes Akathisia Rating Scale (BARS).[92] Another commonly used rating scale is the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale,[92] which is used to assess a variety of antipsychotic-induced side effects, including movement disorders.

The fact that the rating scales are observer-based inherently requires adequate training of clinicians in their use and makes these scales vulnerable to inter-observer variability[93-95], although they have undergone research validation.

Quantitative measurements of EPS in adults

Several studies have used quantitative, objective methods to measure movement disorders induced by antipsychotic drugs. These include instrumental measurements of lingual[96] or finger[97] force variability, handwriting analysis[98;99], 24-hour wrist actigraphy[100], 3-D ultrasonic movement/gait analysis[101], and behavioural pattern monitoring[32]. In general, these quantitative methods are challenging regarding their technical setup and requirement of physical contact with the patient, which make them difficult to implement in a real-world clinical psychiatric setting.

The Kinect sensor

Computerized analysis of human movements has been investigated for more than three decades[102]. Until recently, human motion capture (the process of registering motion) has required an extensive setup, typically involving several cameras, structured light projectors, and special markers attached to the different relevant body parts of the individual being tracked[102]. With the introduction of the Microsoft Kinect in 2010 (Figure 2), a low-cost and accessible human position and motion tracking technology has become available.

Figure 2: The Kinect sensor

Source: https://en.wikipedia.org/wiki/Kinect

The Kinect sensor is a small portable device that combines a regular colour camera with a depth camera and a built-in software based on advanced pattern recognition.[103] The accurate depth camera maps the scene that the Kinect is recording, and the software uses a position-tracking algorithm, enabling it to recognize and track the individual body parts of a person and record their motion. Initially developed as an entertainment device, such as dancing games, the Kinect sensor is now in widespread research use, including neuro-rehabilitation[104], assessment of post-stroke movement impairment[105], and the classification of movements during active video gaming.[106] In surgical navigation, Kinect has been studied to offer an objective method to assess, evaluate and train surgical skills.[107]

The Kinect sensor and software has previously been studied in 9 patients with Parkinson's Disease and 10 healthy controls, showing that it can accurately measure timing and gross spatial characteristics of clinically relevant movements, but without the same spatial accuracy for smaller movements, such as hand clasping.[108] Other research areas applying Kinect to patients with PD are the assessment of gait patterns[109], articulatory movements[110] and lower limb rehabilitation.[111]

Possible advantages of a game-like instrument

Computer games appeal to children and adolescents, and many already use the Kinect and are familiar with interactive computer games. A Chinese pilot study from 2011 of two young adults with motor disabilities showed that the use of a Kinect-based instrument significantly increased their motivation for physical rehabilitation[104].

Schizophrenia has been associated with a disturbance of the sense of self and others, which sometimes makes the experience of physical presence and contact of others threatening to patients[112]. This might challenge patient tolerability to clinician rated clinical assessment, which requires close physical contact. Another typical symptom in schizophrenia is lack of motivation[45]. Compared to healthy controls, persons with schizophrenia show less clinician-rated motivation and perceive less self-reported motivation when they are engaging in an activity[113;114]. A game-like instrument would offer a contact-less and, presumably, an enhanced motivation for evaluation of EPS in patients with schizophrenia and may be an especially attractive measurement method in youth.

Pharmacokinetics of antipsychotics

CYP2D6 polymorphism

Metabolism by the cytochrome P450 (CYP) enzymes is an important pathway of elimination of many drugs. Cytochrome P450 (CYP) enzymes are isoenzymes located in the liver, gut and brain. [115;116] At a hepatic level, they are responsible for catalyzing reductive and oxidative reactions of lipophilic drugs to more hydrophilic products that can be eliminated in urine.[117] CYP2D6 and CYP3A4 play the most important role in oxidative metabolization of antipsychotics[118]. The genes coding for CYP2D6 and CYP3A4 are highly polymorphic.[119;120]

Four CYP2D6 phenotypic subgroups exist, reflecting the degree of CYP2D6 enzymatic activity: Poor metabolizers (PMs) with two null alleles, intermediate metabolizers (IMs) with a combination of either a null allele or two deficient alleles, extensive (normal) metabolizers (EMs) with two normal alleles, and ultra-rapid metabolizers (UMs) with gene duplications or multi-duplications. [117]

Previous studies have consistently shown that plasma serum concentrations of aripiprazole are significantly affected by CYP2D6 genotype.[121-123] PMs are exposed to a 60% higher total aripiprazole drug moieties than EMs. Thus, the FDA label and the Clinical Pharmacogenetics

Implementation Consortium guidelines recommend that PMs are prescribed half the usual dose of aripiprazole.[124] In contrast, the clinical implications of CYP3A4 are not conclusive.[125]

CYP2D6 activity can be further modulated by concomitant use of CYP2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine, quinidine and terbinafine) mimicking a genetic deficiency (phenoconversion), i.e. converting genotypic EM into phenotypic PM of the drug. [126]

Ethnic and geographical variations of the polymorphic expression of CYP2D6 are well-known. Studies have shown that PMs represent 5-10% of Caucasians and 0-19% of Africans, whereas much lower incidences are found in Asians (1%). [127] In a comprehensive study of more than 60.000 individuals across major populations, PM frequencies were the highest in Europeans (5.4%) and lowest in Asians (0.4-1%) and in individuals from the Middle East (0.9%). UMs frequencies were highest in Oceanian (21.2%) and Middle Eastern (11.2%) populations and lowest in individuals from East Asia (1.4%). [128]

Association between CYP2D6 and extrapyramidal symptoms

Interindividual vulnerability to EPS is a well-known problem in clinical practice. Factors contributing to higher drug plasma concentration levels, such as genetic variations in drug-metabolizing enzymes, are likely to increase the risk of EPS development. The association between EPS and CYP2D6 polymorphism have been studied previously, but with conflicting results. [129-135]

Aims and hypothesis

Study I: *CYP2D6 genotyping and antipsychotic-induced extrapyramidal side effects in a randomized trial of aripiprazole versus quetiapine extended release in children and adolescents, aged 12-17, with first-episode psychosis.*

AIMS: To study the association between genetically predicted CYP2D6 phenotype and antipsychotic-induced extrapyramidal symptoms (EPS) in children and adolescents with psychosis

HYPOTHESIS:

We expected to find:

1) A higher dose adjusted plasma concentration of trial drug in the CYP2D6 PM group compared to the IM, EM and UM groups in patients treated with aripiprazole.
2) An association between CYP2D6 genotype groups and global BARS score and SAS scores with highest scores in the PMs in the patients treated with aripiprazole OR clinical dose adjustments of aripiprazole in the PM group.
3) Phenoconversion in patients treated with aripiprazole, i.e. conversion of genotypic EM of aripiprazole into phenotypic PM of aripiprazole (i. e. higher dose adjusted plasma concentration) when concomitant CYP2D6 inhibitors are used.

Study II: *Exploring Movement Impairments in Patients with Parkinson's disease using the Microsoft Kinect Sensor*

AIMS: To develop and test a game-like instrument (*Motorgame*) using the Microsoft Kinect sensor for evaluating performance related bradykinesia and rigidity in patients with idiopathic Parkinson's Disease.

HYPOTHESIS:

1) Higher MDS-UPDRS motor scores (section 3) are associated with a prolonged time of motor performance (of each task in level 1) in the *Motorgame.*
2) Higher SAS rigidity scores and UKU bradykinesia scores are associated with a prolonged time of motor performance (of each task in level 1) in the *Motorgame.*
3) Higher Token Motor Test motor speed scores are associated with a shortened time of motor performance (of each task in level 1) in the *Motorgame.*
4) Higher Symbol Coding Task information processing speed scores are associated with a shortened time of motor performance (of each task in level 1) in the *Motorgame.*

Study III: *Exploring movements in adolescents with psychosis and healthy controls using the Microsoft Kinect sensor – a new tool for assessing antipsychotic-induced parkinsonism?*

AIMS: To test the game-like instrument (*Motorgame*) using the Microsoft Kinect sensor in young patients (n=21) with psychosis and healthy controls (n=69). And to validate this data against scores in established rating scales for clinical motor side effects.

HYPOTHESIS:

1) Higher SAS rigidity scores are associated with a prolonged time of motor performance (of each task in level 1) in the *Motorgame.*
2) Higher Symbol Coding Task information processing speed scores are associated with shorter time of motor performance (of each task in level 1) in the *Motorgame.*
3) A practice effect will be found in both the patient and the healthy control group.

Ethics

As all participants in study I and study III were under 18 years of age at the time of inclusion in the trials, a surrogate written informed consent was required from the holders of custody.

Study I (the TEA trial[136]) was registered at ClinicalTrials.gov: NCT01119014, EudraCT: 2009-016715-38. The TEA trial was approved by Danish Medicines Agency: 2612-4168, The Ethics Committee of Capital Region: H-3-2009-123 and Danish Data Protection Agency: 2009-41-3991.

Study II (Microsoft Kinect sensor trial, adult patients with PD) and study III (Microsoft Kinect sensor trial, youth patients with psychosis) were submitted to The Committees on Health Research Ethics for the Capital Region of Denmark and the Danish Health Authority but did not require mandatory notification. Data collection and storing was approved by The Danish Data Protection Agency (DDPA) journal number 2007-58-0015. DDPA approved the exchange of data with the TEA trial, DDPA journal number 2013-331-0479.

Materials and methods

Study I:

Study I is based on data from the TEA trial, a 12 week, double-blinded and randomised clinical trial investigating efficacy and tolerability of aripiprazole or quetiapine-ER in a youth population with first-episode psychosis. The study was investigator initiated, independently funded, and conducted at six University Hospitals in Denmark. The period of recruitment was June 10th, 2010 to January 29th, 2014.

Participants

Inclusion criteria were:

- Male or female, in- or outpatients aged 12-17 years meeting the ICD-10 criteria[137] for schizophrenia spectrum disorder, delusional disorder, or affective spectrum psychotic disorder.
- A severity of psychosis scoring of ≥4 on at least one of the following Positive and Negative Syndrome Scale (PANSS) items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution) or G9 (unusual thought content); and a total PANSS score of >60 points.
- Antipsychotic-naïve or limited exposure to antipsychotic medication, i.e. maximum 12 months in the past year for psychosis, or no more than one week (lifetime) for non-psychotic indications.

Exclusion criteria were:

- Compulsory treatment, antipsychotic-induced or organic psychosis, severe chronic somatic illness, history of severe head trauma, pregnancy, lactation, substance dependence (ICD-10 F1X.2 dependence syndrome) within the last year, or allergy to aripiprazole, quetiapine-ER or lactose (intolerance).

A titration schedule was followed with target doses of aripiprazole 20 mg/day versus quetiapine-ER 600 mg/day at day 9. However, flexible dosing was allowed (quetiapine: 50-800 mg/day; aripiprazole 2.5-30 mg/day), if needed due to lack of treatment response or adverse effects.

Primary outcome was PANSS positive scores. Key adverse outcomes were body weight, homoeostatic model of insulin resistance, akathisia and sedation.

Assessments

At inclusion, participants were assessed by a program of psychiatric symptom ratings, psychosocial and quality of life ratings, as well as physical examination. Participants were reassessed at follow-up visits at week 2, 4, and 12. Blood sampling and electrocardiography (ECG) recordings were carried out at week 4 and week 12 visits. Patients were genotyped for CYP2D6, and plasma concentrations of concomitant antidepressants (amitriptyline, citalopram, fluoxetine, mianserin, mirtazapine, nortriptypline, sertraline, venlafaxine) and antipsychotics (aripiprazole, chlorprothixene, clozapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone) were analysed.

EPS were assessed by the UKU[138] (a 48-item scale for evaluation of antipsychotic-induced side effects; range 0-3), SAS[139] (a 10-item scale for evaluation of antipsychotic-induced parkinsonism; range 0-4), AIMS[140] (a 10-item scale for evaluation of severity of facial, oral, extremity and trunk dyskinesias; range 0-4), and BARS[141] (a 4-item scale for evaluation of objective and subjective aspects of akathisia; item 1-3 with a range of 0-3; the global score with a range of 0-5).

Statistical analyses

Descriptive analysis and simple group comparisons (aripiprazole versus quetiapine-ER) were performed using Pearson Chi-Square test. Mann-Whitney test was used when comparing median cumulated doses of concomitant antipsychotics. Prior to comparisons, mean plasma concentrations of trial medicine were adjusted for the administered trial medicine dose at the last day prior to laboratory testing. Akathisia cases were defined by a BARS global score $\geq$ 2. Antipsychotic induced parkinsonism cases were defined as mean SAS score $\geq$ 0.33 (as proposed by Simpson et al[139]). Independent t-test was used for between group comparisons of global BARS scores and SAS scores, as well as comparisons between dose adjusted plasma concentrations of aripiprazole when used with or without concomitant sertraline. ANOVA was used to test group differences between CYP2D6 genotype groups and dose adjusted plasma concentrations of aripiprazole, global BARS scores and SAS scores, respectively. Two-sided tests with alpha <0.05 were used and all statistical analyses were made in SPSS (version 22+23).[142;143]

Previously published baseline results and EPS findings in the TEA trial

113 children and adolescent patients with a mean age of 15.7+1.4 years and male proportion of 30.1% were included and randomised to quetiapine-ER (n=55) and aripiprazole (n=58).

At inclusion, approximately half (50.4%) of the patient group was antipsychotic-naïve with no significant difference between study arms. The majority (93%) met the criteria for schizophrenia spectrum psychosis. At baseline, psychiatric symptoms (PANSS) were of moderate intensity, severity of global psychopathology (Clinical Global Impression Severity (CGI-S)) was marked, and psychosocial functioning (Global Assessment of Psychosocial Disability (GAPD)) was seriously reduced in both study arms with no significant between group differences.

In total, numerically more patients in the aripiprazole group (20/58 patients; 34.5%) compared to the quetiapine-ER group (11/55 patient; 20.0%; p=0.085) discontinued trial medication before week 12. Three discontinuations in the aripiprazole group and none in the quetiapine-ER group were entirely due to EPS (two cases of akathisia, one case of hyperkinesia). During trial, no differences in use of antipsychotic co-medication (protocol violation) or anti-depressive medication were seen between treatment arms.

Study II:

Study II is an exploratory study investigating movement impairments in adult patients with Parkinson's Disease versus healthy controls using the Microsoft Kinect sensor. The study was conducted in the Capital Region of Denmark at the Department of Neurology, Bispebjerg University Hospital. Patients were recruited through the department and from private practicing neurologists. Healthy controls were recruited through local tennis clubs, private contacts, and senior centres in the Capitol Region. The period of recruitment was from February 2014 to August 2016.

Participants

Inclusion criteria for the patient group were:

- Male or female, posture stable, i.e. maximal score of 2.5 on the Hoehn & Yahr scale[144], outpatients aged 18 years or above meeting the ICD-10 criteria for idiopathic PD[137;145].

Exclusion criteria for the patient group were:

- Current psychosis, in current antipsychotic treatment and dementia.

Inclusion criteria for the control group were:

- Male or female aged 18 years or above.

Exclusion criteria in the control group were:

- Parkinson's Disease, current psychosis, in current antipsychotic treatment and dementia.

Assessments

Patients were assessed with the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[146]. All participants completed standard neurological examination and assessments by the UKU, SAS and two subtests from the Brief Assessment of Cognition in Schizophrenia (BACS)[147] assessing motor speed (Token Motor Task) and attention and information processing speed (Symbol Coding Task). All participants were assessed by the *Motorgame* and filled out a questionnaire developed by the authors (a 5-point Likert scale assessing their opinion about the *Motorgame* compared to the clinical rating scales and the two BACS subtests).

The Motorgame

The assessment was conducted with the participant placed 2 to 3 meters in front of a computer screen with the Microsoft Kinect sensor attached to it. At the computer screen, the upper body of a stickman figure which mirrored the movement of the participant was shown (see Figure 3). Calibration of the arm length of the stickman was done by asking the participant to stretch out both arms in a vertical position. The participant was then instructed to finish the upcoming tasks as fast and precisely as possible. The *Motorgame* displayed three levels, each introduced by a welcome screen indicating a different task. At each level, the participant repeatedly had to perform similar movements with a random appearance. A real-time score was displayed at the top of the screen with higher scores indicating a fast and correct completion of the subtasks. To avoid interruptions due to questions and unfamiliarity with the game, a training session was performed before data collection. The first two levels are showed in Figure 4 and 5.

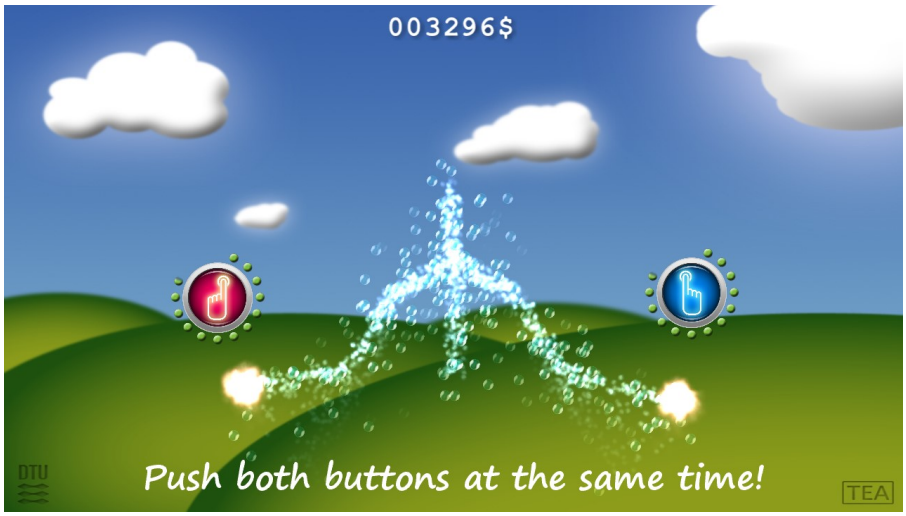
Figure 3.[148] A participant playing the Motorgame.

A Kinect sensor is placed at the top of the screen and tracks the participant's movements. The participant's pose is mirrored as a stickman figure.

Figure 4.[148] Level 1 in the Motorgame from the participant's perspective.

The participant must move his/her right hand upwards to reach the button on the screen.

Figure 5.[148] Level 2 in the Motorgame from the participant perspective.



Now the participant must touch two buttons simultaneously.

Motorgame Data

The individual body parts of the participant were recognized by the depth camera and tracked by the skeletal tracking algorithm of the Microsoft sensor. The data provided by the depth camera with a video stream of 30 frames per second made it possible to estimate the depth of each pixel. The data consisted of a multivariate time-series of measurements, providing positional measurements for wrists, hands, elbows, shoulders, head and neck as 3D coordinates. Data were multivariate time-series of varying length, and a single play of the *Motorgame* generated a large body of data. To avoid overfitting of the model, the only variable extracted for this analysis was the time it took to finish each task in level 1 of the *Motorgame*. For each participant, 22 measurements (tasks) were obtained. This data can be viewed as 22 repeated measurements, but due to the differences of the tasks, e.g. how far the hand had to be moved, they were inherently different. By assigning a fixed effect to each task, this was accounted for in the statistical model.

Statistical analyses

As *Motorgame* data did not fit a Gaussian distribution, natural logarithm transformation was applied. A linear mixed effect model[149] implemented in the package lmer [150] for the R-programming language [151] was used and provided *p*-values for the fixed effects in the model.

Linear mixed effect model used on the data including both fixed effects and random effects:

$$ln(y) = \mu + T_{j+} Cx_{ijC} + Gx_{ijG} + H_{ijH} + Ax_{ijA} + Wx_{ijW} + Sx_{ijS} + \varepsilon_{i+}\varepsilon$$

y: response (natural logarithm of time in seconds it took to finish a single task in level 1)

μ: general mean

T: mean for each of the 22 tasks in level 1

C: parameter for the clinical score

X_{ij} was the value for that measurements on participant *i* in task *j*.

G: gender

H: height

A: age

W: weight

S: Symbol Coding Task

$\varepsilon_{i,}$: random effect for participant *i*

ε: general error (assumed to be independent and identically distributed from a normal distribution).

Study III:

Study III is an exploratory study of young patients with first-episode psychosis versus healthy controls investigating movement patterns. The study was conducted partly at the Centre for Child and Adolescent Mental Health, Mental Health Services (CAMHS), Capital Region of Denmark and partly through the Danish multi-centre TEA trial.[152] Healthy controls were recruited from the TEA trial through a random data extraction from the Danish Centralized Civil Register. The period of recruitment was February 2014 to July 2016.

Participants

Inclusion criteria in the patient group were:

- Male or female, aged 12-19 years, in- or outpatients, fulfilling the ICD-10 criteria for a broad spectrum of young onset psychoses.[137]
- In ongoing (maximal 18 months of treatment) or about to initiate antipsychotic treatment.

Inclusion criteria in the control group were:

- Male or female, aged 12-19 years and physically and mentally healthy.

Assessments

All participants were assessed by clinical, cognitive and neurological examinations. As in study II, assessments included were SAS[91], The UKU[153], Symbol Coding Task and Token Motor Task from

(BACS)[154] and the *Motorgame*. In addition, participants were assessed by the AIMS[90] (assessing dyskinesia) and BARS[92] (assessing akathisia). Healthy controls completed screening with the Kiddie Schedule for Affective Disorders and Schizophrenia Present Lifetime (a semi-structured interview screening for present and previous psychiatric symptoms)[155]. A subgroup of the patients (recruited directly from the clinics at the CAMHS, Capital Region of Denmark) filled in a questionnaire about their opinion of the *Motorgame*. All healthy controls and the patients recruited directly from the CAMHS were re-assessed after 12 weeks. The patients recruited from the TEA trial were reassessed at predefined follow-ups (at week 2, 4, 12 and 52 after randomization to aripiprazole or quetiapine-ER).

Statistical analyses

For the statistical analysis of *Motorgame* data, we used the same linear mixed-effect model as in study II, but with a fixed effect of practice (P) added:

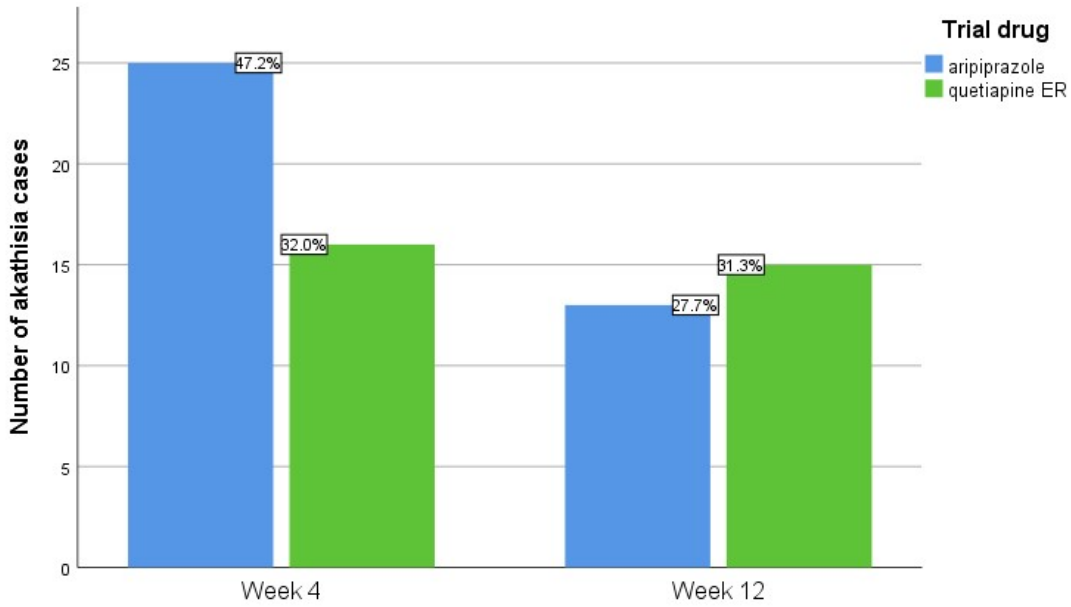
$$ln(y) = \mu + T_{j+} Cx_{ijC} + Gx_{ijG} + H_{ijH} + Ax_{ijA} + Wx_{ijW} + Sx_{ijS} + Px_{ijR+} \varepsilon_{i+} \varepsilon$$

Results

Results from Study I:

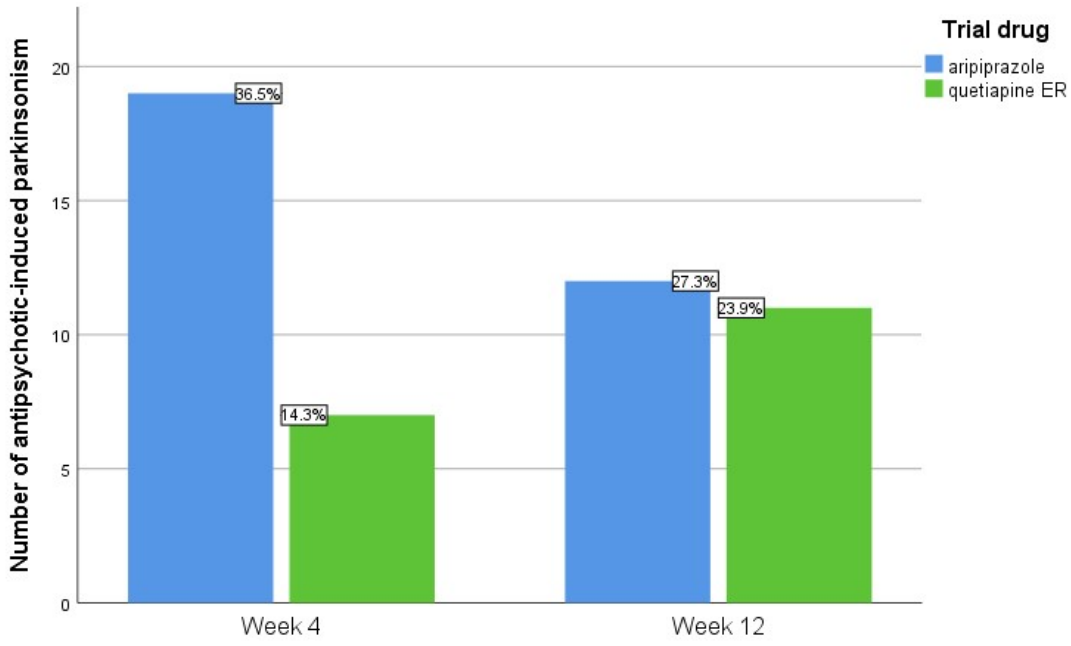
A high incidence of akathisia with no differences between treatment arms was found at week 4 (aripiprazole: 47% versus quetiapine-ER: 32%, p=0.116) and week 12 (aripiprazole: 28% versus quetiapine-ER: 31%; p=0.701)(See Figure 6). In addition, a significantly higher mean global BARS score (±SD) was found in the aripiprazole group at week 4 (1.45±1.19 versus quetiapine-ER: 0.90±1.00; p=0.012), but not at week 12 (aripiprazole: 0.94±1.07 versus quetiapine-ER: 0.94±1.26; p=0.996). In the aripiprazole group, mean global BARS score (±SD) significantly decreased from week 4 to week 12 (p=0.025).

Figure 6. Incidences of akathisia in the TEA trial



The incidence rate of antipsychotic induced parkinsonism was significantly higher in the aripiprazole group at week 4 (37%) compared to the quetiapine-ER group (14%; p=0.011). At week 12, this difference no longer existed (27% in the aripiprazole group versus 24% in the quetiapine-ER group; p=0.715). Likewise, significantly higher levels of mean SAS scores (±SD) were seen at week 4 in the aripiprazole group (0.29 ±0.30) compared to the quetiapine-ER group (0.17 ±0.25; p=0.023). At week 12, the difference had countervailed. Anticholinergic medication, a proxy for antipsychotic-induced parkinsonism, was administered more frequently, but not at a significant level, to aripiprazole-treated patients at week 4 (20% versus 8% in quetiapine-ER-treated patients; p=0.067) and week 12 (12% versus 6% in quetiapine-ER-treated patients; p=0.337). Anti-cholinergic medication was not administered more often in the PM group (table 4).

Figure 7. Incidences of antipsychotic-induced parkinsonism in the TEA trial



Mean dose (±SD) of administered aripiprazole on the last day prior to laboratory testing was 15.05±6.80 mg/day at week 4 and 15.22 mg±7.50 mg at week 12. In the quetiapine-ER group, the mean administered dose (±SD) was 479.55±182.46 mg/day at week 4 and 528.79 mg±181.59 mg/day at week 12. During the 12-week intervention period, 28 patients used different types of concomitant SSRI (sertraline, fluoxetine, citalopram and paroxetine). Only sertraline was verified in the blood samples at week 4 and/or week 12. No difference between dose adjusted aripiprazole concentration (±SD) in patients without concomitant SSRI use (week 4: 36.07±21.74 nmol/L/mg; week 12: 33.07±9.42 nmol/L/mg) compared to patients in concomitant sertraline use (week 4: 35.79±15.25 nmol/L/mg; week 12: 33.48±12.27 nmol/L/mg; p=0.971 and p=0.940, respectively) was found.

One hundred and one patients (89.4%) were CYP2D6 genotyped with an equal distribution between treatment arms.

In the aripiprazole group, CYP2D6 PMs had a significantly higher dose adjusted plasma concentration (±SD) at week 4 (54.20±14.28 nmol/L/mg) and week 12 (49.40±24.61 nmol/L/mg) than EMs at week 4 (33.11 ±13.71 nmol/L/mg) and week 12 (31.93±10.09 nmol/L/mg; p=0.008 and p=0.054) (see table 1 and Figure 8). In addition, borderline significant higher dose adjusted plasma concentration in PMs versus IMs (p=0.097) and UMs (p=0.060) was found at week 4. As we

expected, no association between quetiapine plasma concentration and CYP2D6 genotype groups was found. We did not find any association between CYP2D6 genotype groups and global BARS score, SAS scores or use of anticholinergic medication (table 1).

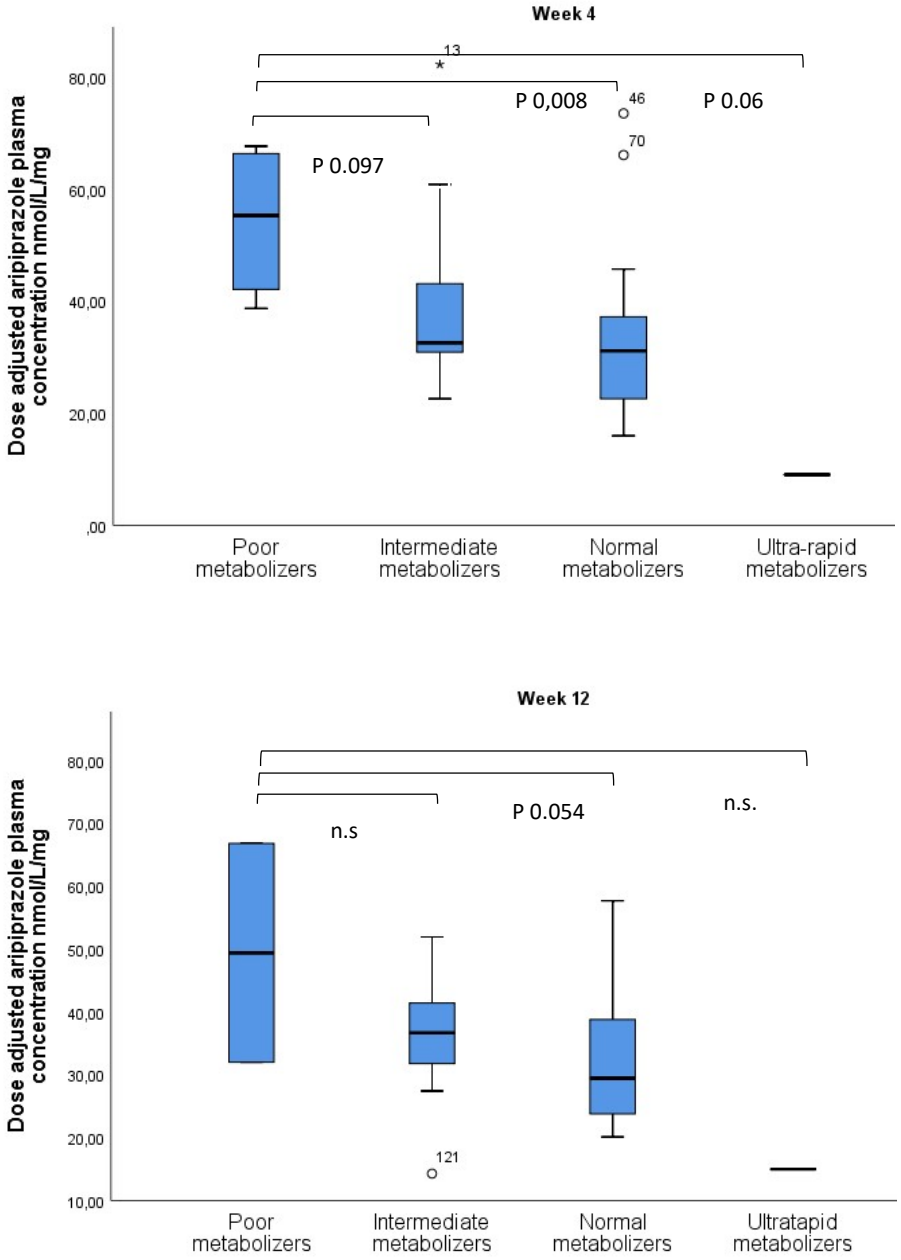
Table 1.[156] Dose adjusted plasma concentrations of trial drug, BARS and SAS scores distributed by CYP2D6 genotype groups

	Poor metabolizers (PM)	Intermediate metabolizers (IM)	Extensive metabolizers (EM)	Ultra-rapid metabolizers (UM)	P value
Aripiprazole group 51 patients with verified genotype					
Patients with valid blood sample, n (%)					
Week 4 (n=45)	4 (8.9)	14 (31.1)	26 (57.8)	1 (2.2)	-
Week 12 (n=32)	2 (6.2)	11 (34.4)	18 (56.3)	1 (3.1)	-
Trial medicine, mean dose*, mg (SD)					
Week 4	16.25 (4.79)	13.93 (6.56)	15.48 (7.42)	20.00 (-)	p=0.785[a]
Week 12	12.50 (3.54)	14.09 (9.17)	15.69 (6.52)	30.00 (-)	p=0.241[a]
Mean plasma concentration/trial medication dose, nmol/l/mg (SD)					
Week 4	54.20 (14.28)	38.50 (16.04)	33.11 (13.71)	9.05 (-)	**p=0.019[a]**
Week 12	49.40 (24.61)	36.15 (10.21)	31.93 (10.09)	15.00 (-)	p=0.067[a]
Use of concomitant anticholinergic medication, n (%)					
Week 4 (n=10)	0 (0.0)	3 (6.7)	7 (15.6)	0 (0.0)	-
Week 12 (n=4)	0 (0.0)	1 (3.1)	3 (9.4)	0 (0.0)	-
Patients with verified genotype and BARS assessment, n (%)					
Week 4 (n=47)	4 (8.5)	16 (34.1)	26 (55.3)	1 (2.1)	-
Week 12 (n=27)	0 (0.0)	11 (40.7)	16 (59.3)	0 (0.0)	-
Global BARS score, mean (SD)					
Week 4	1.25 (0.96)	1.06 (1.24)	1.65 (1.16)	3.00 (-)	p=0.240[a]
Week 12	-	1.00 (1.18)	0.56 (0.96)	-	p=0.301[a]
Patients with verified genotype and SAS assessment, n (%)					
Week 4 (n=46)	4 (8.7)	15 (32.6)	26 (56.5)	1 (2.2)	-
Week 12 (n=25)	0 (0.0)	9 (36.0)	15 (60.0)	1 (4.0)	-
SAS score, mean (SD)					
Week 4	0.18 (0.17)	0.35 (0.33)	0.30 (0.30)	0.30 (-)	p=0.774[a]
Week 12	-	0.20 (0.27)	0.22 (0.19)	0.50 (-)	p=0.450[a]
Quetiapine-ER group 50 patients with verified genotype					

Patients with valid blood sample, n (%)					
Week 4 (n=43)	3 (7.0)	16 (37.2)	23 (53.5)	1 (2.3)	-
Week 12 (n=33)	3 (9.1)	11 (33.3)	19 (57.6)	0 (0.0)	-
Trial medicine, mean dose*, mg (SD)					
Week 4	533.33 (115.47)	550.00 (136.63)	404.35 (189.44)	800.00 (-)	**0.018**[a]
Week 12	600.00 (200.00)	563.64 (80.90)	497.37 (218.88)	-	0.502[a]
Mean plasma concentration/trial medication dose, nmol/l/mg (SD)					
Week 4	2.48 (1.65)	1.79 (1.04)	1.73 (1.21)	1.27 (-)	0.733[a]
Week 12	2.42 (1.43)	1.17 (0.50)	1.47 (1.15)	-	0.179[a]
Use of concomitant anticholinergic medication, n (%)					
Week 4 (n=4)	1 (2.3)	0 (0.0)	3 (7.0)	0 (0.0)	-
Week 12 (n=3)	1 (3.0)	0 (0.0)	2 (6.1)	0 (0.0)	-
Patients with verified genotype and BARS assessment, n (%)					
Week 4 (n=40)	3 (7.5)	15 (37.5)	22 (55.0)	0 (0.0)	-
Week 12 (n=34)	3 (8.8)	12 (35.3)	19 (55.9)	0 (0.0)	-
Global BARS score, mean (SD)					
Week 4	1.00 (1.00)	1.00 (1.20)	1.14 (0.94)	-	0.920[a]
Week 12	1.33 (1.53)	0.58 (1.00)	0.95 (1.47)	.	0.616[a]
Patients with verified genotype and SAS assessment, n (%)					
Week 4 (n=39)	3 (7.7)	15 (38.5)	21 (53.8)	0 (0.0)	-
Week 12 (n=32)	3 (9.4)	12 (37.5)	17 (53.1)	0 (0.0)	-
SAS score, mean (SD)					
Week 4	0.33 (0.42)	0.13 (0.14)	0.19 (0.30)	-	0.474[a]
Week 12	0.20 (0.26)	0.20 (0.23)	0.19 (0.19)	-	0.997[a]

Note: SD Standard Deviation; BARS Barnes Akathisia Rating Scale; SAS Simpson Angus Scale; ER Extended Release; a ANOVA between group differences;
* Trial medicine dose on the last day prior to laboratory testing; - Not applicable

Figure 8.[156] Boxplot of dose adjusted plasma concentration of aripiprazole distributed by genetically predicted Cytochrome 450 2D6 phenotypes at week 4 and week 12



Note: n.s. non-significant

Results from Study II:

Thirty patients with Parkinson's Disease and 33 healthy controls were included with a mean age (±SD) of 70.1±6.7 years in the patient group versus 69.7±6.1 years in the healthy group (p=0.787). The patient group had significantly more males than the control group (60% versus 30%, p=0.018).

Patients had a mean (±SD) PD duration of 45.7±34.0 months and used a daily mean L-dopa (L-3,4-dihydroxyphenylalanine) equivalent dose[157] (±SD) of 868.4±1,902.2 mg.

Due to the use of a log transformation of the Motorgame response data (table 2), the parameter estimates from the model cannot be related directly to changes in seconds. However, the parameter estimates can be seen as percentwise increase/decrease in time to finish the tasks.

For instance, table 2 shows that every time the Rigidity Neck score is raised by 1 point, the time it takes for the participant to finish the Motorgame tasks is prolonged by ($e^{0.0401} = 1.0409 - 1 = 0.0409$) 4% compared to a participant of same gender, age, height, weight and score in Symbol Coding Task (table 2).

Within the group of patients with PD, a statistically significant ($p<0.05$) association between prolonged time of motor performance in the *Motorgame* and upper body rigidity and bradykinesia (measured by the MDS-UPDRS) was found. The strongest effects were seen in the right hand (finger tapping right hand, hand movements right hand, and rotation of right hand; ($p<0.001$); table 2).

Table 2.[148] The effect of motor items in the MDS-UPDRS (section 3) on the time of motor performance in the *Motorgame*.

	MDS-UPDRS score	Gender (male)	Age (years)	Height (metres)	Weight (kilograms)	Symbol Coding Task score
3.3a Rigidity Neck	**0.0401*** (0.0191)	-0.105 (0.0524)	-0.000552 (0.00307)	0.00517 (0.00349)	-0.00132 (0.00174)	**-0.00555**** (0.00161)
3.3b Rigidity Right Arm	**0.0447*** (0.0185)	-0.0994 (0.051)	0.000343 (0.00306)	0.00542 (0.00343)	-0.00136 (0.00171)	**-0.00509**** (0.00162)
3.3c Rigidity Left Arm	0.0372 (0.019)	-0.0916 (0.0516)	0.000325 (0.00313)	0.00525 (0.00351)	-0.00133 (0.00175)	**-0.0051**** (0.00167)
3.3d Rigidity Right Leg	**0.0351*** (0.0156)	-0.0946 (0.0511)	-0.000163 (0.00306)	0.00543 (0.00346)	-0.00174 (0.00171)	**-0.00508**** (0.00164)
3.3e Rigidity Left Leg	**0.0364*** (0.0165)	-0.0876 (0.0509)	-0.000624 (0.00306)	0.00515 (0.00348)	-0.00159 (0.00171)	**-0.00497**** (0.00166)
3.4a Finger Tapping Right Hand	**0.0528**** (0.0149)	**-0.135**** (0.0502)	0.000949 (0.00291)	**0.00799*** (0.00328)	-0.00203 (0.0016)	**-0.00517**** (0.0015)
3.4b Finger Tapping Left Hand	0.0308 (0.0161)	-0.103 (0.0527)	-0.000768 (0.00309)	0.00581 (0.00349)	-0.00114 (0.00177)	**-0.00562**** (0.00161)
3.5a Hand Movements Right	**0.0583**** (0.0162)	**-0.116*** (0.0486)	0.00106 (0.0029)	**0.00757*** (0.00325)	-0.00163 (0.0016)	**-0.00508**** (0.0015)
3.5b Hand Movements Left	0.024 (0.0167)	-0.0872 (0.0523)	-0.000534 (0.00314)	0.00546 (0.00357)	-0.00123 (0.00181)	**-0.00567**** (0.00165)
3.6a Pronation-Supination Movements of Hands Right	**0.06**** (0.0163)	**-0.12*** (0.0486)	0.00066 (0.00287)	**0.00804*** (0.00326)	-0.002 (0.00159)	**-0.0053**** (0.00149)
3.6b Pronation-Supination Movements of Hands Left	**0.0302*** (0.0148)	-0.0841 (0.0511)	-0.000763 (0.00308)	0.00535 (0.00349)	-0.00129 (0.00174)	**-0.00564**** (0.0016)
3.12 Postural Stability	0.0201 (0.0229)	-0.0839 (0.053)	-0.000243 (0.00321)	0.00642 (0.00359)	-0.00183 (0.00178)	**-0.00601**** (0.00164)
3.13 Posture	0.0438 (0.0218)	-0.0969 (0.0519)	-0.00101 (0.00308)	0.00592 (0.00348)	-0.00145 (0.00174)	**-0.00573**** (0.0016)
3.14 Global Spontaneity of Movement (Body Bradykinesia)	**0.0419*** (0.0183)	**-0.111*** (0.0525)	-0.000369 (0.00305)	0.00515 (0.00347)	-0.000732 (0.00178)	**-0.00517**** (0.00163)

Since MDS-UPDRS was only assessed in patients with Parkinson's Disease all controls have been assigned value zero for the measured variables in this analysis.

Results are logtransformed (natural logaritme). Each parameter estimate is presented with the standard deviation in parenthesis (SD). * $p<0.05$; ** $p<0.001$.

In the entire group, prolonged time of motor performance in the *Motorgame* was significantly associated with higher SAS rigidity score and higher UKU hypokinesia scores ($p<0.05$; table 3).

As seen in table 3, every time the SAS-1 score is raised by 1 point, the time it takes for the participant to finish the Motorgame tasks is prolonged by ($e^{0.0613} = 1.0632 - 1 = 0.0632$) 6% compared to a participant of same gender, age, height, weight and score in Symbol Coding Task (table 3).

A shortened time of motor performance in the *Motorgame* was significantly associated with higher information processing speed (Symbol Coding Task) ($p<0.001$).

As can be seen in table 3, every time the Symbol Code score is raised by 1 point, the time it takes the participant to finish the Motorgame tasks is shortened by ($e^{-0.0046} = 0.9954 - 1 = - 0.0046$) 0.5% compared to a participant of same gender, age, height, weight and score in SAS-1.

No association was found between time of motor performance and Token Motor Task, duration of PD, or hours of daily physical activity.

The patients had a longer, but not significantly so, motor performance time in the *Motorgame* compared to the healthy controls (estimate$\pm$SD 0.058$\pm$0.032; $p>0.05$).

The questionnaire data showed that the *Motorgame* was well accepted and preferred by the majority of patients (53%) and healthy controls (76%).

Table 3.[148] The effect of clinical assessment scores (Simpson Angus Scale, UKU and Token Motor task) and disease related characteristics on the time of motor performance in the *Motorgame*.

	Clinical assessment Score	Gender (male)	Age (years)	Height (metres)	Weight (kilograms)	Symbol Coding Task score
SAS-1 Gait	**0.0613* (0.025)**	**-0.1028* (0.051)**	-0.00004 (0.003)	0.0050 (0.003)	-0.0008 (0.002)	**-0.0046* (0.002)**
SAS-2 Arm drop	**0.0717* (0.024)**	-0.0938 (0.049)	-0.0009 (0.003)	0.0040 (0.003)	-0.0009 (0.002)	**-0.0046* (0.002)**
SAS-3 Shoulder shaking	**0.0766* (0.023)**	**-0.1016* (0.049)**	-0.0001 (0.003)	0.0041 (0.0033)	-0.0008 (0.002)	**-0.0044*(0.002)**
SAS-4 Elbow rigidity	**0.0441*(0.017)**	**-0.1044* (0.051)**	0.0002 (0.003)	0.0053 (0.003)	-0.0012 (0.002)	**-0.0052* (0.002)**
SAS-5 Wrist rigidity	**0.0742* (0.026)**	**-0.1020* (0.050)**	-0.0004 (0.003)	0.0052 (0.003)	-0.0014 (0.002)	**-0.0053* (0.002)**
SAS-6 Leg pendulousness	**0.0369*(0.013)**	-0.0955 (0.050)	-0.0006 (0.003)	0.0051 (0.003)	-0.0013 (0.002)	**-0.0053* (0.002)**
SAS-7 Head dropping	**0.0431* (0.019)**	**-0.1071* (0.052)**	-0.0007 (0.003)	0.0051 (0.003)	-0.0012 (0.002)	**-0.0056** (0.002)**
SAS-8 Glabella tap	**0.0323* (0.011)**	-0.0813 (0.051)	0.0005 (0.003)	0.0046 (0.004)	-0.0010 (0.002)	**-0.0049* (0.002)**
SAS-9 Tremor	0.0162 (0.018)	-0.0824 (0.053)	-0.0010 (0.003)	0.0059 (0.004)	-0.0019 (0.002)	**-0.0061** (0.002)**
SAS-10 Salivation	0.0987 (0.056)	-0.0929 (0.052)	-0.0002 (0.003)	0.0061 (0.004)	-0.0014 (0.002)	**-0.0056* (0.002)**
2.3 Hypokinesia (UKU)	**0.0665* (0.022)**	**-0.1128* (0.050)**	-0.0008 (0.003)	0.0047 (0.003)	-0.0002 (0.002)	**-0.0052* (0.002)**
Token Motor Task	-0.0012 (0.001)	-0.0852 (0.054)	-0.0005 (0.003)	0.0061 (0.004)	-0.0017 (0.002)	**-0.0054*(0.002)**
Duration of Parkinson	0.0009 (0.000)	-0.1010 (0.053)	-0.0000 (0.003)	0.0072 (0.003)	-0.0018 (0.002)	**-0.0056*(0.002)**
Physical activity	0.0001 (0.003)	-0.0791 (0.054)	-0.0006 (0.003)	0.0062 (0.004)	-0.0019 (0.002)	**-0.0061** (0.002)**

Results are logtransformed (natural logaritme). Each parameter estimate is presented with the standard deviation in parenthesis.

Duration of Parkinson's Disease (PD) is in months. Physical activity is average number of hours per week. * $p<0.05$; ** $p<0.001$.

Results from Study III:

Twenty-one adolescent patients with psychosis (62% treated with antipsychotics and 38% antipsychotic-näive) and 69 adolescent healthy controls were included in the study. Age (mean age 16±1.4 years in patient group versus 16±1.5 years in control group; no significant group difference) and gender distribution (38% males in patient group versus 36% in control group; no significant group difference) were equal in the two groups. Overall, the clinical rating scale scores of EPS were higher, and severity predominantly mild, and in a few cases moderate, in the patient group compared to the group of healthy controls, but only at a significant level when comparing the SAS scores of the antipsychotic-medicated patients (n=9) with the healthy controls (n=50) (p=0.048). No participants experienced dystonia or dyskinesia. Antipsychotic-naïve patients (n=8) performed significantly worse in the Token Motor Task (45.4±18.5 points; p<0.001) and in the Symbol Coding Task (55.1±17.3 points; p=0.016) compared to the healthy controls (n=69; 67.9±15.1 points and 66.4±11.6 points, respectively).

A significant association between prolonged time of motor performance in the *Motorgame* and higher SAS-scores for arm dropping (p=0.009) was found, as well as a consistent practice effect for the *Motorgame* (p<0.001) (table 4). However, arm dropping would not have survived a Bonferroni correction (corrected p-value <0.005), given the 10 tests in the SAS rating scale.

Table 4 shows that every time the SAS score for arm dropping is raised by 1 point, the time it takes the participant to finish the *Motorgame* tasks is prolonged by ($e^{-0.069} = 1.0714 - 1 = 0.0714$) 7.1% compared to a participant of same gender, age, height, weight, score in Symbol Coding Task and effect of repetition. As can be seen in Table 4, a participant was approximately 2.5-2.9% faster to finish the *Motorgame* tasks at time of repetition compared a participant of the same SAS score, gender, age, height, weight and score in Symbol Coding Task (table 4).

Surprisingly, shortened time of motor performance was associated with higher scores of glabella tap (p<0.001).

Lower Symbol Coding Task (lower information processing speed) scores were associated with prolonged time of motor performance in the *Motorgame*, but only at a significant level (p<0.05) when testing for arm dropping, shoulder shaking and glabella tap. The patients had a longer, but not significantly so, motor performance time in the *Motorgame* compared to the healthy controls (estimate±SD 0.0003±0.0204; p=0.990).

No significant associations between performances of the *Motorgame* and age, height, body weight, gender, or information processing speed were detected. Based on the responses from the questionnaire (n=8), the *Motorgame* was well accepted (88% reported the instrument easy/very easy to use and 75% reported fun/very fun to use) and was preferred above assessment with clinical rating scales by 38%.

Table 4.[158] The effect of Simson Angus Scale items on the time of motor performance in the Kinect *Motorgame*

Model	SAS score	Gender (male)	Age (years)	Height (metres)	Weight (kilograms)	Symbol Coding Task score	Repetition
SAS-1 Gait, value±SD	0.053±0.038	0.025±0.018	-0.001±0.005	0.002±0.001	-0.001±0.001	-0.001±0.001	**-0.029±0.006****
SAS-2 Arm dropping, value±SD	**0.069±0.026***	0.027±0.017	-0.000±0.005	0.001±0.001	-0.001±0.001	**-0.001±0.000***	**-0.025±0.006****
SAS-3 Shoulder shaking, value±SD	0.017±0.015	0.029±0.017	-0.001±0.005	0.001±0.001	-0.001±0.001	**-0.001±0.000***	**-0.028±0.006****
SAS-4 Elbow rigidity, value±SD	-0.001±0.015	0.026±0.018	-0.001±0.005	0.001±0.001	-0.001±0.001	-0.001±0.000	**-0.028±0.006****
SAS-5: Wrist rigidity, value±SD	0.035±0.036	0.029±0.018	-0.001±0.005	0.001±0.001	-0.001±0.001	-0.001±0.000	**-0.028±0.006****
SAS-6: Leg pendulousness, value±SD	0.021±0.028	0.027±0.017	-0.001±0.005	0.001±0.001	-0.001±0.001	-0.001±0.000	**-0.028±0.006****
SAS-7: Head dropping, value±SD	-0.015±0.021	0.025±0.018	-0.001±0.005	0.001±0.001	-0.001±0.001	-0.001±0.000	**-0.028±0.006****
SAS-8: Glabella tap, value±SD	**-0.020±0.006****	0.033±0.018	-0.001±0.005	0.002±0.001	-0.001±0.001	**-0.001±0.001***	**-0.027±0.006****
SAS-9: Tremor, value±SD	-0.014±0.008	0.026±0.018	-0.001±0.005	0.001±0.001	-0.001±0.001	-0.001±0.000	**-0.025±0.006****
SAS-10: Salivation, value±SD	-0.014±0.021	0.026±0.017	-0.001±0.005	0.001±0.001	-0.001±0.001	-0.001±0.000	**-0.029±0.006****

Mixed model analysis. Results are logtransformed (natural logaritme). Each parameter estimate is presented with the standard deviation (±SD). * $p<0.05$; ** $p<0.001$.

Discussion

Antipsychotic use in the pediatric population has been increasing over the past decades[159-163]. This includes on-label use, but also a concerning off-label use which is associated with further increased risks of side effects and under- or overdosing due to lack of pharmacokinetic data.[164;165] Since the introduction of SGAs in the 1980s, focus of concern regarding side effects have shifted from EPS, which were prominent with FGAs, to cardiometabolic side effects with increased long-term risk of diabetes mellitus and cardiovascular disease.[166-170] But as studies show, the risk of EPS in SGAs is not negligible, neither in adults[33;37-39] nor in children and adolescents.[44-46]

In study I, we found a high proportion of akathisia cases in children and adolescent patients with first-episode of psychosis, especially initially after four weeks of antipsychotic treatment (aripiprazole: 47% versus quetiapine-ER: 32%, p=0.116), but also, albeit to a lesser degree, at week 12 (aripiprazole: 28% versus quetiapine-ER: 31%; p=0.701). Usually, much lower incidences for youth are reported in the literature: 6-15% for aripiprazole and 0-6% for quetiapine.[34] Possible explanations might be the combination of a very intensive i.e. more precise and correct BARS monitoring on a regular basis. An alternative explanation could be the difficulty of distinguishing symptoms of akathisia from resembling symptoms such as anxiety, agitation and general restlessness, which might have led to an overestimation of akathisia. Additionally, a significantly higher global BARS score was found in the aripiprazole arm compared to the quetiapine-ER arm at week 4, which supports previous findings from a systematic review with pairwise and network meta-analyses of antipsychotics for treatment of patients with first-episode schizophrenia, showing that quetiapine was associated with less akathisia compared to aripiprazole, haloperidol, risperidone and olanzapine[171]. Interestingly, our results indicate that akathisia is especially prominent initially, but appears to wear off over time despite unchanged dose of aripiprazole and quetiapine-ER throughout the study. In the quetiapine-ER group, the administered mean dose was even slightly increased from week 4 to week 12. This is in line with findings from a randomised comparison of risperidone and aripiprazole in adults with first-episode schizophrenia in which akathisia was found to be a temporary side effect.[172] Furthermore, a significantly higher incidence of antipsychotic-induced parkinsonism (37% versus 14%, p=0.011) as well as a significantly higher mean SAS score was found at week 4 in the aripiprazole arm (0.29$\pm$0.30 versus 0.17$\pm$0.25; p=0.023). Both differences between treatment arms had countervailed at week 12. The results are

comparable to the incidence rates (rigidity/any parkinsonian event in aripiprazole group 14-30% and quetiapine group 0-27%) reported in a previous review of 34 studies of children and adolescents with psychosis or bipolar spectrum disorders treated with SGA.[34]

It is a well-established fact that the steady state concentrations of aripiprazole are significantly dependent on the number of the mutated alleles of the CYP2D6 locus .[121;173-175] As expected, we found that poor CYP2D6 metabolizers had a significantly higher dose-adjusted aripiprazole plasma concentration compared to extensive metabolizers at week 4 and at week 12. Not surprisingly, this association was not found in the quetiapine-ER group, since quetiapine is mainly metabolized by CYP3A4

The association between EPS and CYP2D6 polymorphism has previously been studied but results are conflicting. [78] In a study of 62 antipsychotic-treated inpatients, Vandel and colleagues found a higher percentage of PMs in the group of patients with EPS (n=22) than the group of patients without such side effects (n=43) ($P < 0.00001$).[129] Schillevoort and colleagues showed that antipsychotic-treated PMs in their case-control study had a 4.44 (OR; 95% confidence interval (CI) 1.11-17.68) times higher risk of initiating anticholinergic medication (proxy for EPS) compared to EMs. [130] In a study of 267 patients in antipsychotic treatment, 29 patients with EPS and 188 without EPS, a significant association between PMs (OR 4.1; 95% CI 1.01-16; p= 0.01) and IMs (OR 5.4; 95% CI 1.13-18; p= 0.003) and the risk of EPS was found.[131] A systematic review of CYP testing by Fleeman and colleagues showed that PMs were significantly more likely to develop parkinsonism than EMs (OR 1.64; 95% CI 1.04-2.58).[176] Armstrong and colleagues found a difference, although not significant, between the incidence of EPS in the group of PMs (80%, 4 out of 5 patients) compared to the remaining patients with EPS (44%, 31 patients out of 71 patients). [133] In contrast, no significant differences in CYP2D6 genotype groups between patients with and without EPS in a study of 119 patients with schizophrenia was detected by Scordo and colleagues.[134] In a study of 131 patients with schizophrenia or schizoaffective disease, Plesnicar and colleagues found no significant difference between PMs and other groups regarding EPS.[135] Despite the fact that poor metabolizers of CYP2D6 were associated with increased plasma concentrations in our study, we did not find any associations between CYP2D6 genotype groups and global BARS score or SAS score in any of the treatment arms. This might be explained by the considerable overlap between dose adjusted plasma aripiprazole concentrations between PM, IM, EM and UMs (Figure 8), showing the significant interindividual differences in dose-effect

relationships of antipsychotics. Another confounder could have been phenoconversion, i.e. concomitant intake of CYP2D6 inhibitors converting EMs to PMs.[177] Sertraline was the only concomitant CYP2D6 inhibiting drug verified in the blood samples at week 4 and week 12. We did not find any phenoconversion when comparing patients in the aripiprazole treatment arm with and without concomitant SSRI use.

The main strength of study I is the randomised, double-blind design with the EPS ratings done unbiased. The study uses a semi-forced titration scheme with a subsequent flexible dosing, which makes it comparable to clinical practice. The study also had methodological limitations. We did not have a wash-out period for the 38.9% of the patients with (a limited) antipsychotic exposure prior to randomization, thus risking a carry-over effect. However, subgroup analysis in antipsychotic naïve patients and the group of patients with a limited antipsychotic exposure, did not reveal any significant differences at baseline in the mean BARS or SAS scores. The analyses in this study were done post hoc and non-blinded (in contrast to the previously published results[178]). The clinical rating scales used have not been validated in children. In adults, solid evidence of reliability and validity has been established, both regarding BARS[179;180] and SAS.[181] The study was primarily designed to investigate efficacy and therefore not powered to detect clinically relevant differences in genetic subpopulations. Hence, the number of PMs was small making it difficult to detect clinically relevant differences, increasing the risk of type I and type II errors. Concomitant medication was allowed during the intervention, which reflects normal daily clinical practice, but also increases the risk of confounding effects. Finally, interrater reliability testing was only carried out for PANSS ratings (primary outcome) and not for the EPS assessments. However, only nurses and doctors experienced in child and adolescent psychiatry and well-trained in the use of the side effects rating scales were involved in the EPS assessments.

Until recently, computerized analysis of movement patterns required both extensive and expensive equipment. In 2010, a low-cost human motion tracking technology was introduced with the Microsoft Kinect, originally developed for motion recognition in gaming (Xbox 360).[182]

In study II, the *Motorgame* (game-like instrument using the Microsoft Kinect software and sensor) was tested and proven able to detect bradykinesia in PD. Detection and quantification of bradykinesia is of clinical importance since bradykinesia has been shown to strongly correlate with a broad spectrum of PD motor deficits including gait, posture and distal motor problems.[183] In

addition, 18 F-DOPA PET brain scans in PD patients indicate significant correlation between hypokinesia and rigidity motor symptoms and dopaminergic depletion in the striatum[184].

In the group of adult patients with PD, we found significant associations between prolonged time of motor performance in the *Motorgame* and upper-body rigidity and bradykinesia (MDS-UPDRS) with the strongest effects related to right hand movements. This finding is in line with a previous study of patients with Parkinson's Disease and healthy controls by Galna and colleagues. They studied Microsoft Kinect data against a Vicon three-dimensional motion analysis system and found that the timing of repetitive shoulder and elbow movements based on UPDRS III (motor rating)[185] was measured very accurately.[108] In study II, we found significant associations between time of motor performance and bradykinesia and rigidity in the clinical rating scales: i.e. prolonged time of motor performance in the *Motorgame* was related to higher rigidity SAS scores and UKU hypokinesia. However, we did not find a significant association between time of motor performance in the *Motorgame* (assessing gross motor skills) and motor speed in the Token Motor Task, which might be due to the fact that the *Motorgame* demands a high level of eye-hand coordination and cognitive skills compared to the Token Motor Task, in which patients are given 100 plastic tokens and asked to place them two at a time into a container as quickly as possible within 60 seconds.[154] Correspondingly, we found a significant moderating effect of the Symbol Coding Task on the time of performance of the *Motorgame* (i.e. shortened time of performance was associated with better scores in information processing).

Males had a significantly faster performance time in the majority of estimates, which is consistent with findings in motor performance in healthy individuals[186]. Due to the small sample size it is not possible to analyze whether this difference is further accentuated by the illness of PD.

Furthermore, we did not find an association between time of motor performance in the *Motorgame* and the duration of illness. A possible explanation might be that the patients in this study were all well-medicated with a relatively short mean (±SD) duration of illness of 45.7 months $\pm$ 34.0 months and a median Hoehn and Yahr score of 2. Likewise, and probably for the same reasons, no significant difference in the time of motor performance in the *Motorgame* between patients with PD and healthy controls was found, even though patients were approximately 6% slower.

The *Motorgame* was well accepted in both patients and healthy participants, which is in line with a previous study of adaptive training and rehabilitation using the Microsoft sensor in patients with PD.[187]

The applicability of the *Motorgame* to the clinical setting was tested and proven on several levels. The *Motorgame* was easy to set up in hospitals, in private houses, in tennis clubs and senior centers and in hospitals. The Microsoft Kinect sensor and a portable computer were easily operated and did not require expert knowledge to use. The *Motorgame* displayed an appropriate complexity, since all PD participants and healthy controls completed the assessment. A previous study indicates that videogames for patients with PD should not have too high cognitive demands regarding decision-making, response inhibition, divided attention and working memory.[188] Including healthy controls made us able to match data on age, but unfortunately not on gender, two important variables in motor performance[186].

Study II has methodological limitations. Since the *Motorgame* only covers neck and upper extremities, further development is needed to improve the tracking of tremor and motor symptoms in the lower extremities in future studies.

The Kinect version used did not have the accuracy to detect tremors, at least not based on the motion trajectories computed by the internal Kinect algorithms. Tremor related measurements could possibly be extracted from the raw depth-image data, but due to the small the sample size experimental data exploration was not possible, and tremor related clinical measurements were excluded from the analysis.

The sample size of study II was small, thereby enhancing the risk of type I and type II errors.

Due to the risk of overfitting the sparse set of movement related features such as speed, acceleration and deceleration, we chose to do the analysis on a simple meta-variable (the playing time), even though the system is able to gather very large amounts of data from the movement patterns.

In study III the *Motorgame* was tested in a group of children and adolescent patients with first-episode psychosis and healthy controls. To our knowledge the Microsoft Kinect has not previously been studied in this study population. Studies in other young patient groups (with motor disabilities[104], hemiplegic cerebral palsy[189] and cystic fibrosis[190]) show that the Kinect sensor

enhances motivation and is preferred for its interactivity. Likewise, the *Motorgame* was found easy and fun to use and accepted by participants in our study.

As expected, we found significantly lower level of parkinsonism SAS scores in healthy controls compared to antipsychotic medicated patients. In addition, motor speed scores (Token Motor Task) were significantly lower in both antipsychotic-unmedicated and antipsychotic-medicated patients compared to the healthy controls. Parkinsonian motor impairment has previously been documented in antipsychotic-naïve patients with first-episode schizophrenia and in their unaffected, first-degree relatives.[191-195] The highest severity of parkinsonian motor impairment was found in affected patients, intermediate severity was found in unaffected relatives, and nearly absent in healthy controls.[196;197] Furthermore, we found that information processing speed (Symbol Coding Task) was significantly lower in both antipsychotic-unmedicated and antipsychotic-medicated patients compared to the healthy controls. This is in line with previous findings in adult patients with schizophrenia.[154]

We found a significant association, albeit uncorrected for multiple comparisons, between prolonged time of motor performance in the *Motorgame* and bradykinesia in the shoulders of the participants. Since none of the other five closely related SAS rigidity items (shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness or head dropping) displayed significant effects, this result may have been due to a type I error owing to small sample size and multiple testing. Validation and reliability studies of the Simpson Angus scale have demonstrated good internal consistency with Cronbach's alpha coefficients of 0.79-0.93 [198;199] [200]. However, the non-significance of our findings could be due to type II error, also related to the small sample size.

As also shown in study II, higher information processing speed (lower Symbol Coding Task scores) was significantly associated with shorter time of motor performance in the *Motorgame* at a significant level ($p<0.05$). This result is in line with a study of memory in non-medicated adult patients with schizophrenia, in which Fervaha and colleagues showed the severity of parkinsonism (assessed by SAS) to be reliably linked with poorer scores on tests of cognition (verbal memory**,** processing speed, and working.[201]

As expected for this age group, a consistent and clear practice effect was found.

Surprisingly, and in contrast to the results in study II, we found a significant negative effect of glabella tap on the time of motor performance in the *Motogame*. All participants with an abnormal glabella tap were found in the patient group, except from one healthy control (with a

score of 1=mild). The glabellar reflex is a behavioral motor response found in neonates, which is subsequently inhibited before the age of 5 years.[202] An abnormal glabellar reflex is primarily seen in diffuse cerebral hemisphere vascular and degenerative diseases [203]. Glabellar tap is in general considered to be non-specific, non-diagnostic, and a poor measure of Parkinson motor severity, and is no longer used in clinical neurology for the assessment of Parkinsonism [204]. Some studies have shown a poor intercorrelation between glabella tap and the other items of parkinsonism in the SAS [200;205]. Our finding is most likely explained by a type I error (false positive) due to the small sample size, since no theoretical reasons or study results currently support such an association.

No significant associations between motor performances on the *Motorgame* and age, height, body weight, gender, or information processing speed were detected.

No significant difference in the time used on motor performance between patients and healthy controls was found. This finding may be due to the low proportion of first-episode psychosis patients in the study as well as the relatively low severity of motor side effects.

Study III has, apart from the strengths and limitations already mentioned, the advantage of studying practice effects, a measure relevant for repeated measurements in clinical practice. The similarities of the *Motorgame* to an ordinary computer game and the reduced time of physical contact with the physician are factors expected to increase the patient's willingness to participate. Unfortunately, the *Motorgame* covers only a part of the clinical examination of antipsychotic parkinsonism, hence it remains untested whether the *Motorgame* can detect tremor and dyskinesia.

Clinical perspectives and future research

Based on the relatively high rates of antipsychotic-induced parkinsonism and akathisia and low rates of dystonia and dyskinesia found in our study, close and careful monitoring of EPS is needed in clinical practice, since these symptoms predict poorer outcome and treatment non-compliance in patients with psychosis. Our findings do not support routine CYP2D6 genotyping to detect patients with increased susceptibility to antipsychotic-induced EPS in children and adolescents with first-episode psychosis. Long-term studies with clinical rating scales validated for children and adolescents are needed.

We developed and tested a game-like instrument (*Motorgame*) using the Microsoft Kinect sensor to evaluate performance related bradykinesia and rigidity. The *Motorgame* was able to detect such symptoms in PD and bradykinesia in the shoulders of children and adolescents.

The *Motorgame* offered a well-accepted, feasible and objective system to complement the traditional observer-based rating scales in a clinical meaningful way. However, further development of the *Motorgame* is needed to improve tracking of tremor and motor symptoms in lower extremities. A new non-gaming version of the Microsoft Kinect 'Azure Kinect' has been released to the market recently, which probably has an even better potential for the detecting tremors.[206] In addition, larger scale studies are needed based on the SD found in our studies. Studies with this kind of objective, contactless instrument for assessing movement disorders would also be highly relevant in other patient groups within psychiatry, i.e. patients with pervasive developmental disorder, autism spectrum disorders or intellectual disability, as well as patients with schizophrenia suffering from catatonia. The technology holds the potential for future for quantitative, in-hospital assessments, but also for in-home use, allowing the patient to provide automated reports to the neurologist or psychiatrist.

References

Reference List

(1) Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet* 2016; 388(10039):86-97.

(2) Harvey PD. Assessing disability in schizophrenia: tools and contributors. *J Clin Psychiatry* 2014; 75(10):e27.

(3) McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev* 2008; 30:67-76.

(4) Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005; 2(5):e141.

(5) Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG et al. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophr Bull* 2018.

(6) Androutsos C. [Schizophrenia in children and adolescents: relevance and differentiation from adult schizophrenia]. *Psychiatriki* 2012; 23 Suppl 1:82-93.

(7) Maloney AE, Yakutis LJ, Frazier JA. Empirical evidence for psychopharmacologic treatment in early-onset psychosis and schizophrenia. *Child Adolesc Psychiatr Clin N Am* 2012; 21(4):885-909.

(8) Remschmidt H, Theisen F. Early-onset schizophrenia. *Neuropsychobiology* 2012; 66(1):63-69.

(9) Ropcke B, Eggers C. Early-onset schizophrenia: a 15-year follow-up. *Eur Child Adolesc Psychiatry* 2005; 14(6):341-350.

(10) Fleischhaker C, Schulz E, Tepper K, Martin M, Hennighausen K, Remschmidt H. Long-term course of adolescent schizophrenia. *Schizophr Bull* 2005; 31(3):769-780.

(11) Remschmidt H, Martin M, Fleischhaker C, Theisen FM, Hennighausen K, Gutenbrunner C et al. Forty-two-years later: the outcome of childhood-onset schizophrenia. *J Neural Transm (Vienna)* 2007; 114(4):505-512.

(12) Clemmensen L, Vernal DL, Steinhausen HC. A systematic review of the long-term outcome of early onset schizophrenia. *BMC Psychiatry* 2012; 12.

(13) Vyas NS, Patel NH, Puri BK. Neurobiology and phenotypic expression in early onset schizophrenia. *Early Interv Psychiatry* 2011; 5(1):3-14.

(14) Rapoport JL, Inoff-Germain G. Update on childhood-onset schizophrenia. *Curr Psychiatry Rep* 2000; 2(5):410-415.

(15) Clemmensen L, Vernal DL, Steinhausen HC. A systematic review of the long-term outcome of early onset schizophrenia. *BMC Psychiatry* 2012; 12:150.

(16) Wilcox JA, Reid DP. The Syndrome of Catatonia. *Behav Sci (Basel)* 2015; 5(4):576-588.

(17) AYD FJ, Jr. A survey of drug-induced extrapyramidal reactions. *JAMA* 1961; 175:1054-1060.

(18) Wirshing WC. Movement disorders associated with neuroleptic treatment. *J Clin Psychiatry* 2001; 62 Suppl 21:15-18.

(19) Raja M. Managing antipsychotic-induced acute and tardive dystonia. *Drug Saf* 1998; 19(1):57-72.

(20) Caroff SN, Campbell EC. Drug-Induced Extrapyramidal Syndromes: Implications for Contemporary Practice. *Psychiatr Clin North Am* 2016; 39(3):391-411.

(21) Casey DE. Motor and mental aspects of extrapyramidal syndromes. *Int Clin Psychopharmacol* 1995; 10 Suppl 3:105-114.

(22) Shirzadi AA, Ghaemi SN. Side effects of atypical antipsychotics: extrapyramidal symptoms and the metabolic syndrome. *Harv Rev Psychiatry* 2006; 14(3):152-164.

(23) Thanvi B, Treadwell S. Drug induced parkinsonism: a common cause of parkinsonism in older people. *Postgrad Med J* 2009; 85(1004):322-326.

(24) Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. *Schizophr Res* 1999; 35 Suppl:S61-S66.

(25) Rana AQ, Chaudry ZM, Blanchet PJ. New and emerging treatments for symptomatic tardive dyskinesia. *Drug Des Devel Ther* 2013; 7:1329-1340.

(26) Buchanan A. A two-year prospective study of treatment compliance in patients with schizophrenia. *Psychol Med* 1992; 22(3):787-797.

(27) Perkins DO. Predictors of noncompliance in patients with schizophrenia. *J Clin Psychiatry* 2002; 63(12):1121-1128.

(28) Frances A, Weiden P. Promoting compliance with outpatient drug treatment. *Hosp Community Psychiatry* 1987; 38(11):1158-1160.

(29) Kim JH, Kim MJ. Association of adverse drug effects with subjective well-being in patients with schizophrenia receiving stable doses of risperidone. *Clinical neuropharmacology* 2009; 32(5).

(30) Novak L, Svab V. Antipsychotics side effects' influence on stigma of mental illness: focus group study results. *Psychiatr Danub* 2009; 21(1):99-102.

(31) Sachdev P. Early extrapyramidal side-effects as risk factors for later tardive dyskinesia: a prospective study. *Aust N Z J Psychiatry* 2004; 38(6):445-449.

(32) Caligiuri MR, Jeste DV, Lacro JP. Antipsychotic-Induced movement disorders in the elderly: epidemiology and treatment recommendations. *Drugs & aging* 2000; 17(5).

(33) Abou-Setta AM, Mousavi SS, Spooner C, Schouten JR, Pasichnyk D, Armijo-Olivo S et al. 2012.

(34) Fraguas D, Correll CU, Merchan-Naranjo J, Rapado-Castro M, Parellada M, Moreno C et al. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. *Eur Neuropsychopharmacol* 2011; 21(8):621-645.

(35) Patten SB, Waheed W, Bresee L. A review of pharmacoepidemiologic studies of antipsychotic use in children and adolescents. *Can J Psychiatry* 2012; 57(12):717-721.

(36) Panagiotopoulos C, Ronsley R, Elbe D, Davidson J, Smith DH. First do no harm: promoting an evidence-based approach to atypical antipsychotic use in children and adolescents. *J Can Acad Child Adolesc Psychiatry* 2010; 19(2):124-137.

(37) Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* 2008; 371(9618):1085-1097.

(38) Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull* 2012; 38(1):167-177.

(39) Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013; 382(9896):951-962.

(40) Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019; 394(10202):939-951.

(41) Divac N, Prostran M, Jakovcevski I, Cerovac N. Second-generation antipsychotics and extrapyramidal adverse effects. *Biomed Res Int* 2014; 2014:656370.

(42) Weiden PJ. EPS profiles: the atypical antipsychotics are not all the same. *J Psychiatr Pract* 2007; 13(1):13-24.

(43) Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. *Journal of the American Academy of Child and Adolescent Psychiatry* 2008; 47(1).

(44) Cohen D, Bonnot O, Bodeau N, Consoli A, Laurent C. Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis. *Journal of clinical psychopharmacology* 2012; 32(3).

(45) Bernagie C, Danckaerts M, Wampers M, De HM. Aripiprazole and Acute Extrapyramidal Symptoms in Children and Adolescents: A Meta-Analysis. *CNS Drugs* 2016; 30(9):807-818.

(46) Carbon M, Kapoor S, Sheridan E, Al-Jadiri A, Azzo S, Sarkaria T et al. Neuromotor Adverse Effects in 342 Youth During 12 Weeks of Naturalistic Treatment With 5 Second-Generation Antipsychotics. *J Am Acad Child Adolesc Psychiatry* 2015; 54(9):718-727.

(47) Pagsberg AK, Tarp S, Glintborg D, Stenstrom AD, Fink-Jensen A, Correll CU et al. Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis. *J Am Acad Child Adolesc Psychiatry* 2017; 56(3):191-202.

(48) Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chaimani A et al. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. *Eur Neuropsychopharmacol* 2018; 28(6):659-674.

(49) Pillay J, Boylan K, Carrey N, Newton A, Vandermeer B, Nuspl M et al. 2017.

(50) LABORIT H, HUGUENARD P. [Artificial hibernation by pharmacodynamic and physical means, in surgery]. *J Chir (Paris)* 1951; 67(8-9):631-641.

(51) HAMON, PARAIRE, VELLUZ. [Effect of R. P. 4560 on maniacal agitation]. *Ann Med Psychol (Paris)* 1952; 110(1 3):331-335.

(52) DELAY J, DENIKER P, ROPERT R. [Study of 300 case histories of psychotic patients treated with chlorpromazine in closed wards since 1952]. *L'Encephale* 1956; 45(4):528-535.

(53) Shen WW. Pharmacotherapy of schizophrenia: the American current status. *Keio J Med* 1994; 43(4):192-200.

(54) Hippius H. The history of clozapine. *Psychopharmacology (Berl)* 1989; 99 Suppl:S3-S5.

(55) Idanpaan-Heikkila J, Alhava E, Olkinuora M, Palva IP. Agranulocytosis during treatment with chlozapine. *Eur J Clin Pharmacol* 1977; 11(3):193-198.

(56) Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; 45(9):789-796.

(57) Mailman RB, Murthy V. Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? *Curr Pharm Des* 2010; 16(5):488-501.

(58) Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* 1976; 261(5562):717-719.

(59) Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Arch Gen Psychiatry* 1992; 49(7):538-544.

(60) STECK H. [Extrapyramidal and diencephalic syndrome in the course of largactil and serpasil treatments]. *Ann Med Psychol (Paris)* 1954; 112(2 5):737-744.

(61) Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. *Arch Gen Psychiatry* 2000; 57(6):553-559.

(62) Seeman P. Atypical antipsychotics: mechanism of action. *Can J Psychiatry* 2002; 47(1):27-38.

(63) Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. *J Pharmacol Exp Ther* 1989; 251(1):238-246.

(64) Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. *Am J Psychiatry* 2001; 158(3):360-369.

(65) Meltzer HY, Li Z, Kaneda Y, Ichikawa J. Serotonin receptors: their key role in drugs to treat schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27(7):1159-1172.

(66) Horacek J, Bubenikova-Valesova V, Kopecek M, Palenicek T, Dockery C, Mohr P et al. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS Drugs* 2006; 20(5):389-409.

(67) Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. *CNS Drugs* 2004; 18(4):251-267.

(68) Ichikawa J, Meltzer HY. Relationship between dopaminergic and serotonergic neuronal activity in the frontal cortex and the action of typical and atypical antipsychotic drugs. *Eur Arch Psychiatry Clin Neurosci* 1999; 249 Suppl 4:90-98.

(69) Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. *J Pharmacol Exp Ther* 1989; 251(1):238-246.

(70) Seeman P. Dopamine D2 receptors as treatment targets in schizophrenia. *Clin Schizophr Relat Psychoses* 2010; 4(1):56-73.

(71) Yokoi F, Grunder G, Biziere K, Stephane M, Dogan AS, Dannals RF et al. Dopamine D2 and D3 receptor occupancy in normal humans treated with the antipsychotic drug aripiprazole (OPC 14597): a study using positron emission tomography and [11C]raclopride. *Neuropsychopharmacology* 2002; 27(2):248-259.

(72) Natesan S, Reckless GE, Nobrega JN, Fletcher PJ, Kapur S. Dissociation between in vivo occupancy and functional antagonism of dopamine D2 receptors: comparing aripiprazole to other antipsychotics in animal models. *Neuropsychopharmacology* 2006; 31(9):1854-1863.

(73) Burris KD, Molski TF, Xu C, Ryan E, Tottori K, Kikuchi T et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther* 2002; 302(1):381-389.

(74) Citrome L, Josiassen R, Bark N, Salazar DE, Mallikaarjun S. Pharmacokinetics of aripiprazole and concomitant lithium and valproate. *J Clin Pharmacol* 2005; 45(1):89-93.

(75) Winans E. Aripiprazole. *Am J Health Syst Pharm* 2003; 60(23):2437-2445.

(76) Saller CF, Salama AI. Seroquel: biochemical profile of a potential atypical antipsychotic. *Psychopharmacology (Berl)* 1993; 112(2-3):285-292.

(77) Thyrum PT, Wong YW, Yeh C. Single-dose pharmacokinetics of quetiapine in subjects with renal or hepatic impairment. *Prog Neuropsychopharmacol Biol Psychiatry* 2000; 24(4):521-533.

(78) Caccia S. Biotransformation of post-clozapine antipsychotics: pharmacological implications. *Clin Pharmacokinet* 2000; 38(5):393-414.

(79) Bakken GV, Rudberg I, Christensen H, Molden E, Refsum H, Hermann M. Metabolism of quetiapine by CYP3A4 and CYP3A5 in presence or absence of cytochrome B5. *Drug Metab Dispos* 2009; 37(2):254-258.

(80) DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet* 2001; 40(7):509-522.

(81) Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin Pharmacol Ther* 1997; 61(3):331-339.

(82) Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology* 2009; 72(21 Suppl 4):S1-136.

(83) Wichmann T, DeLong MR. Anatomy and physiology of the basal ganglia: relevance to Parkinson's disease and related disorders. *Handb Clin Neurol* 2007; 83:1-18.

(84) Prescott IA, Liu LD, Dostrovsky JO, Hodaie M, Lozano AM, Hutchison WD. Lack of depotentiation at basal ganglia output neurons in PD patients with levodopa-induced dyskinesia. *Neurobiology of disease* 2014; 71c.

(85) Winge K. Lower urinary tract dysfunction in patients with parkinsonism and other neurodegenerative disorders. Handb.Clin.Neurol. 2015. 335-356.

(86) Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord* 2014; 29(13):1583-1590.

(87) Hausner RS. Neuroleptic-induced parkinsonism and Parkinson's disease: differential diagnosis and treatment. *J Clin Psychiatry* 1983; 44(1):13-16.

(88) Caroff SN, Hurford I, Lybrand J, Campbell EC. Movement disorders induced by antipsychotic drugs: implications of the CATIE schizophrenia trial. *Neurologic clinics* 2011; 29(1).

(89) Knol W, Keijsers CJ, Jansen PA, van Marum RJ. Systematic evaluation of rating scales for drug-induced parkinsonism and recommendations for future research. *Journal of clinical psychopharmacology* 2010; 30(1).

(90) Guy WNIoMHPRBECDEP. Abnormal Involuntary Movement Scale (AIMS). In: Guy W, editor. Rockville, Md.: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.

(91) Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta psychiatrica Scandinavica Supplementum* 1970; 212.

(92) Barnes TR. A rating scale for drug-induced akathisia. *The British journal of psychiatry : the journal of mental science* 1989; 154.

(93) Wolff AL, O'Driscoll GA. Motor deficits and schizophrenia: the evidence from neuroleptic-naive patients and populations at risk. *Journal of psychiatry & neuroscience : JPN* 1999; 24(4).

(94) Lohr JB, Caligiuri MP. Quantitative instrumental measurement of tardive dyskinesia: a review. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 1992; 6(4).

(95) Dean CE, Russell JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments: how do they compare in assessing abnormal, involuntary movements? *Journal of clinical psychopharmacology* 2004; 24(3).

(96) Koning JP, Tenback DE, Kahn RS, Van Schelven LJ, Van Harten PN. Instrument measurement of lingual force variability reflects tardive tongue dyskinesia. *Journal of medical engineering & technology* 2010; 34(1).

(97) Caligiuri MP, Lohr JB. Fine force instability: a quantitative measure of neuroleptic-induced dyskinesia in the hand. *The Journal of neuropsychiatry and clinical neurosciences* 1990; 2(4).

(98) Caligiuri MP, Teulings HL, Dean CE, Niculescu AB, Lohr J. Handwriting movement analyses for monitoring drug-induced motor side effects in schizophrenia patients treated with risperidone. *Human movement science* 2009; 28(5).

(99) Caligiuri MP, Teulings HL, Dean CE, Niculescu AB3, Lohr JB. Handwriting movement kinematics for quantifying extrapyramidal side effects in patients treated with atypical antipsychotics. *Psychiatry research* 2010; 177(1-2).

(100) Walther S, Koschorke P, Horn H, Strik W. Objectively measured motor activity in schizophrenia challenges the validity of expert ratings. *Psychiatry research* 2009; 169(3).

(101) Putzhammer A, Klein HE. Quantitative analysis of motor disturbances in schizophrenic patients. *Dialogues in clinical neuroscience* 2006; 8(1).

(102) Perry W, Minassian A, Paulus MP, Young JW, Kincaid MJ, Ferguson EJ et al. A reverse-translational study of dysfunctional exploration in psychiatric disorders: from mice to men. *Archives of general psychiatry* 2009; 66(10).

(103) Bonnechere B, Jansen B, Salvia P, Bouzahouene H, Omelina L, Moiseev F et al. Validity and reliability of the Kinect within functional assessment activities: comparison with standard stereophotogrammetry. *Gait & posture* 2014; 39(1).

(104) Chang YJ, Chen SF, Huang JD. A Kinect-based system for physical rehabilitation: a pilot study for young adults with motor disabilities. *Research in developmental disabilities* 2011; 32(6).

(105) Olesh EV, Yakovenko S, Gritsenko V. Automated Assessment of Upper Extremity Movement Impairment due to Stroke. *PLoS One* 2014; 9(8).

(106) Rosenberg M, Thornton AL, Lay BS, Ward B, Nathan D, Hunt D et al. Development of a Kinect Software Tool to Classify Movements during Active Video Gaming. *PLoS One* 2016; 11(7):e0159356.

(107) Svendsen MB, Preisler L, Hillingsoe JG, Svendsen LB, Konge L. Using motion capture to assess colonoscopy experience level. *World J Gastrointest Endosc* 2014; 6(5).

(108) Galna B, Barry G, Jackson D, Mhiripiri D, Olivier P, Rochester L. Accuracy of the Microsoft Kinect sensor for measuring movement in people with Parkinson's disease. *Gait Posture* 2014; 39(4):1062-1068.

(109) Arango Paredes JD, Munoz B, Agredo W, Ariza-Araujo Y, Orozco JL, Navarro A. A reliability assessment software using Kinect to complement the clinical evaluation of Parkinson's disease. *Conf Proc IEEE Eng Med Biol Soc* 2015; 2015:6860-6863.

(110) Bandini A, Orlandi S, Giovannelli F, Felici A, Cincotta M, Clemente D et al. Markerless Analysis of Articulatory Movements in Patients With Parkinson's Disease. *J Voice* 2015.

(111) Palacios-Navarro G, Garcia-Magarino I, Ramos-Lorente P. A Kinect-Based System for Lower Limb Rehabilitation in Parkinson's Disease Patients: a Pilot Study. *J Med Syst* 2015; 39(9):103.

(112) Nelson B, Whitford TJ, Lavoie S, Sass LA. What are the neurocognitive correlates of basic self-disturbance in schizophrenia?: Integrating phenomenology and neurocognition. Part 1 (Source monitoring deficits). *Schizophr Res* 2014; 152(1):12-19.

(113) Luther L, Firmin RL, Lysaker PH, Minor KS, Salyers MP. A meta-analytic review of self-reported, clinician-rated, and performance-based motivation measures in schizophrenia: Are we measuring the same "stuff"? *Clin Psychol Rev* 2018; 61:24-37.

(114) Trémeau F, Goldman J, Antonius D, Javitt DC. Inpatients with schizophrenia report impaired situational motivation but intact global and social motivation. *Psychiatry research* 2013; 210(1).

(115) Kapur BM, Lala PK, Shaw JL. Pharmacogenetics of chronic pain management. *Clin Biochem* 2014; 47(13-14):1169-1187.

(116) Chinta SJ, Pai HV, Upadhya SC, Boyd MR, Ravindranath V. Constitutive expression and localization of the major drug metabolizing enzyme, cytochrome P4502D in human brain. *Brain Res Mol Brain Res* 2002; 103(1-2):49-61.

(117) Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther* 2013; 17(3):165-184.

(118) Buur-Rasmussen B, Brosen K. Cytochrome P450 and therapeutic drug monitoring with respect to clozapine. *Eur Neuropsychopharmacol* 1999; 9(6):453-459.

(119) Yang Y, Botton MR, Scott ER, Scott SA. Sequencing the CYP2D6 gene: from variant allele discovery to clinical pharmacogenetic testing. *Pharmacogenomics* 2017; 18(7):673-685.

(120) Ingelman M DANDeal. The human cytochrome P450 (CYP) allele nomenclature database [Homepage Committee HCPAN]. Available at: http://www.cypalleles.ki.se.Accessed January 8, 2013 . 2020. 5-3-2012.
Ref Type: Online Source

(121) Hendset M, Hermann M, Lunde H, Refsum H, Molden E. Impact of the CYP2D6 genotype on steady-state serum concentrations of aripiprazole and dehydroaripiprazole. *Eur J Clin Pharmacol* 2007; 63(12):1147-1151.

(122) Lisbeth P, Vincent H, Kristof M, Bernard S, Manuel M, Hugo N. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. *Eur J Clin Pharmacol* 2016; 72(2):175-184.

(123) van der Weide K, van der Weide J. The Influence of the CYP3A4*22 Polymorphism and CYP2D6 Polymorphisms on Serum Concentrations of Aripiprazole, Haloperidol, Pimozide, and Risperidone in Psychiatric Patients. *J Clin Psychopharmacol* 2015; 35(3):228-236.

(124) Food and Drug Administration (ed). Aripiprazole label ; 2017. Aripiprazole (ABILIFY) drug label. https://www.pharmgkb.org/chemical/PA10026/label/PA166104839. 2017.
Ref Type: Online Source

(125) Tornio A, Backman JT. Cytochrome P450 in Pharmacogenetics: An Update. *Adv Pharmacol* 2018; 83:3-32.

(126) Shah RR, Smith RL. Addressing phenoconversion: the Achilles' heel of personalized medicine. *Br J Clin Pharmacol* 2015; 79(2):222-240.

(127) Xie HG, Kim RB, Wood AJ, Stein CM. Molecular basis of ethnic differences in drug disposition and response. *Annu Rev Pharmacol Toxicol* 2001; 41:815-850.

(128) Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder JS. Prediction of CYP2D6 phenotype from genotype across world populations. *Genet Med* 2017; 19(1):69-76.

(129) Vandel P, Haffen E, Vandel S, Bonin B, Nezelof S, Sechter D et al. Drug extrapyramidal side effects. CYP2D6 genotypes and phenotypes. *Eur J Clin Pharmacol* 1999; 55(9):659-665.

(130) Schillevoort I, de BA, van der Weide J, Steijns LS, Roos RA, Jansen PA et al. Antipsychotic-induced extrapyramidal syndromes and cytochrome P450 2D6 genotype: a case-control study. *Pharmacogenetics* 2002; 12(3):235-240.

(131) Crescenti A, Mas S, Gasso P, Parellada E, Bernardo M, Lafuente A. Cyp2d6*3, *4, *5 and *6 polymorphisms and antipsychotic-induced extrapyramidal side-effects in patients receiving antipsychotic therapy. *Clin Exp Pharmacol Physiol* 2008; 35(7):807-811.

(132) Fleeman N, Dundar Y, Dickson R, Jorgensen A, Pushpakom S, McLeod C et al. Cytochrome P450 testing for prescribing antipsychotics in adults with schizophrenia: systematic review and meta-analyses. *Pharmacogenomics J* 2011; 11(1):1-14.

(133) Armstrong M, Daly AK, Blennerhassett R, Ferrier N, Idle JR. Antipsychotic drug-induced movement disorders in schizophrenics in relation to CYP2D6 genotype. *Br J Psychiatry* 1997; 170:23-26.

(134) Scordo MG, Spina E, Romeo P, Dahl ML, Bertilsson L, Johansson I et al. CYP2D6 genotype and antipsychotic-induced extrapyramidal side effects in schizophrenic patients. *Eur J Clin Pharmacol* 2000; 56(9-10):679-683.

(135) Plesnicar BK, Zalar B, Breskvar K, Dolzan V. The influence of the CYP2D6 polymorphism on psychopathological and extrapyramidal symptoms in the patients on long-term antipsychotic treatment. *J Psychopharmacol* 2006; 20(6):829-833.

(136) Pagsberg AK, Jeppesen P, Klauber DG, Jensen KG, Ruda D, Stentebjerg-Olesen M et al. Quetiapine versus aripiprazole in children and adolescents with psychosis--protocol for the randomised, blinded clinical Tolerability and Efficacy of Antipsychotics (TEA) trial. *BMC Psychiatry* 2014; 14.

(137) The ICD-10 Classification of Mental and Behavioral Disorders. Clinical and Diagnostic guidelines. 1992.

(138) Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987; 334:1-100.

(139) Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970; 212:11-19.

(140) Guy W. Abnormal Involuntary Movement Scale (AIMS). Rockville, National Institute of Mental Health. 1976.

(141) Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989; 154:672-676.

(142) IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. 2013.
Ref Type: Online Source

(143) IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. 2015.
Ref Type: Online Source

(144) Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17(5):427-442.

(145) Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015; 30(12):1591-1601.

(146) Goetz CG TBSSSGFSM-MPeal. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Movement disorder: official journal of the Movement Disorder Society . 2008.
Ref Type: Magazine Article

(147) Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res* 2004; 68(2-3):283-297.

(148) Rudå D EG, Andersen ASS MJCCWKCLPRPAF-JA. Exploring Movement Impairments in Patients with Parkinson's disease using the Microsoft Kinect Sensor. 2020.
Ref Type: Online Source

(149) McLean R.A. SWLSWW. A unified approach to mixed linear models. *Am Stat* 1991; 45:54-64.

(150) Kuznetsova ABPBCRHB. lmerTest: tests for random and fixed effects for linear mixed effect models (lmer objects of lme4 package). http://CRAN.R-project.org/package=lmerTest . 2013.
Ref Type: Online Source

(151) Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.2013. 2014.
Ref Type: Online Source

(152) Pagsberg AK, Jeppesen P, Klauber DG, Jensen KG, Ruda D, Stentebjerg-Olesen M et al. Quetiapine versus aripiprazole in children and adolescents with psychosis--protocol for the randomised, blinded clinical Tolerability and Efficacy of Antipsychotics (TEA) trial. *BMC Psychiatry* 2014; 14:199.

(153) Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta psychiatrica Scandinavica Supplementum* 1987; 334.

(154) Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res* 2004; 68(2-3):283-297.

(155) Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997; 36(7):980-988.

(156) Rudå D, Jensen KG, Decara MS, Fagerlund B, Jepsen JRM, Linnet K et al. CYP2D6 genotyping and antipsychotic-induced extrapyramidal side effects in a randomized trial of aripiprazole versus quetiapine extended release in children and adolescents, aged 12-17 years, with first episode psychosis. 2020.
Ref Type: Online Source

(157) Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010; 25(15):2649-2653.

(158) Rudå D, Einarson G, Matthiassen J, Correll C, Jensen KGKD, Richard C et al. Measuring movements in adolescents with psychosis using the Microsoft Kinect sensor: a pilot study exploring a new tool for assessing aspects of antipsychotic-induced parkinsonism. Child and Adolescent Mental Health.https://doi.org/10.1111/camh.12360.E-pub ahead of print. 2020.
Ref Type: Online Source

(159) Cooper WO, Hickson GB, Fuchs C, Arbogast PG, Ray WA. New users of antipsychotic medications among children enrolled in TennCare. *Arch Pediatr Adolesc Med* 2004; 158(8):753-759.

(160) Olfson M, Blanco C, Liu SM, Wang S, Correll CU. National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Archives of general psychiatry* 2012; 69(12).

(161) Rodday AM, Parsons SK, Correll CU, Robb AS, Zima BT, Saunders TS et al. Child and adolescent psychiatrists' attitudes and practices prescribing second generation antipsychotics. *J Child Adolesc Psychopharmacol* 2014; 24(2):90-93.

(162) Birnbaum ML, Saito E, Gerhard T, Winterstein A, Olfson M, Kane JM et al. Pharmacoepidemiology of antipsychotic use in youth with ADHD: trends and clinical implications. *Curr Psychiatry Rep* 2013; 15(8):382.

(163) Olfson M, King M, Schoenbaum M. Treatment of Young People With Antipsychotic Medications in the United States. *JAMA Psychiatry* 2015; 72(9):867-874.

(164) Sohn M, Moga DC, Blumenschein K, Talbert J. National trends in off-label use of atypical antipsychotics in children and adolescents in the United States. *Medicine (Baltimore)* 2016; 95(23):e3784.

(165) Gore R, Chugh PK, Tripathi CD, Lhamo Y, Gautam S. Pediatric Off-Label and Unlicensed Drug Use and Its Implications. *Curr Clin Pharmacol* 2017; 12(1):18-25.

(166) Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M, Rejas J. Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS Study. *Schizophr Res* 2007; 90(1-3):162-173.

(167) Correll CU, Kane JM, Manu P. Obesity and coronary risk in patients treated with second-generation antipsychotics. *Eur Arch Psychiatry Clin Neurosci* 2011; 261(6):417-423.

(168) Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med* 2011; 17(2):97-107.

(169) Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 2009; 302(16):1765-1773.

(170) Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry* 2014; 71(12):1350-1363.

(171) Zhu Y, Krause M, Huhn M, Rothe P, Schneider-Thoma J, Chaimani A et al. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses. *Lancet Psychiatry* 2017; 4(9):694-705.

(172) Robinson DG, Gallego JA, John M, Petrides G, Hassoun Y, Zhang JP et al. A Randomized Comparison of Aripiprazole and Risperidone for the Acute Treatment of First-Episode Schizophrenia and Related Disorders: 3-Month Outcomes. *Schizophr Bull* 2015; 41(6):1227-1236.

(173) Kim JR, Seo HB, Cho JY, Kang DH, Kim YK, Bahk WM et al. Population pharmacokinetic modelling of aripiprazole and its active metabolite, dehydroaripiprazole, in psychiatric patients. *Br J Clin Pharmacol* 2008; 66(6):802-810.

(174) Suzuki T, Mihara K, Nakamura A, Nagai G, Kagawa S, Nemoto K et al. Effects of the CYP2D6*10 allele on the steady-state plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, in Japanese patients with schizophrenia. *Ther Drug Monit* 2011; 33(1):21-24.

(175) Hendset M, Molden E, Knape M, Hermann M. Serum concentrations of risperidone and aripiprazole in subgroups encoding CYP2D6 intermediate metabolizer phenotype. *Ther Drug Monit* 2014; 36(1):80-85.

(176) Fleeman N, Dundar Y, Dickson R, Jorgensen A, Pushpakom S, McLeod C et al. Cytochrome P450 testing for prescribing antipsychotics in adults with schizophrenia: systematic review and meta-analyses. *Pharmacogenomics J* 2011; 11(1):1-14.

(177) Kiss A, Menus A, Toth K, Deri M, Sirok D, Gabri E et al. Phenoconversion of CYP2D6 by inhibitors modifies aripiprazole exposure. *Eur Arch Psychiatry Clin Neurosci* 2020; 270(1):71-82.

(178) Pagsberg AK, Jeppesen P, Klauber DG, Jensen KG, Ruda D, Stentebjerg-Olesen M et al. Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: the multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. *Lancet Psychiatry* 2017.

(179) Barnes TR. The Barnes Akathisia Rating Scale--revisited. *J Psychopharmacol* 2003; 17(4):365-370.

(180) Janno S, Holi MM, Tuisku K, Wahlbeck K. Actometry and Barnes Akathisia Rating Scale in neuroleptic-induced akathisia. *Eur Neuropsychopharmacol* 2005; 15(1):39-41.

(181) Knol W, Keijsers CJ, Jansen PA, van Marum RJ. Systematic evaluation of rating scales for drug-induced parkinsonism and recommendations for future research. *J Clin Psychopharmacol* 2010; 30(1):57-63.

(182) Pham A. "E3: Microsoft shows off gesture control technology for Xbox 360". The effort aims to attract a broader audience to Microsoft's console. Most of the 30 million Xbox 360s sold since November 2005 have been snapped up by avid young males drawn to complex shooter or adventure games such as Halo and Modern Warfare or R.P.Gs. Los Angeles Times . 6-1-2009.
Ref Type: Online Source

(183) Nieuwboer A, De WW, Dom R, Lesaffre E. A frequency and correlation analysis of motor deficits in Parkinson patients. *Disabil Rehabil* 1998; 20(4):142-150.

(184) Pikstra ARA, van der Hoorn A, Leenders KL, de Jong BM. Relation of 18-F-Dopa PET with hypokinesia-rigidity, tremor and freezing in Parkinson's disease. *Neuroimage Clin* 2016; 11:68-72.

(185) Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement disorders : official journal of the Movement Disorder Society* 2008; 23(15).

(186) Jimenez-Jimenez FJ, Calleja M, Alonso-Navarro H, Rubio L, Navacerrada F, Pilo-de-la-Fuente B et al. Influence of age and gender in motor performance in healthy subjects. *J Neurol Sci* 2011; 302(1-2):72-80.

(187) Summa S, Basteris A, Betti E, Sanguineti V. Adaptive training with full-body movements to reduce bradykinesia in persons with Parkinson's disease: a pilot study. *J Neuroeng Rehabil* 2015; 12:16.

(188) dos Santos Mendes FA, Pompeu JE, Modenesi LA, Guedes da SK, Oliveira TP, Peterson ZA et al. Motor learning, retention and transfer after virtual-reality-based training in Parkinson's disease--effect of motor and cognitive demands of games: a longitudinal, controlled clinical study. *Physiotherapy* 2012; 98(3):217-223.

(189) Rammer JR, Krzak JJ, Riedel SA, Harris GF. Evaluation of upper extremity movement characteristics during standardized pediatric functional assessment with a Kinect(R)-

based markerless motion analysis system. *Conf Proc IEEE Eng Med Biol Soc* 2014; 2014:2525-2528.

(190) Salonini E, Gambazza S, Meneghelli I, Tridello G, Sanguanini M, Cazzarolli C et al. Active Video Game Playing in Children and Adolescents With Cystic Fibrosis: Exercise or Just Fun? *Respir Care* 2015; 60(8):1172-1179.

(191) Caligiuri MP, Lohr JB, Jeste DV. Parkinsonism in neuroleptic-naive schizophrenic patients. *Am J Psychiatry* 1993; 150(9):1343-1348.

(192) Chakos MH, Mayerhoff DI, Loebel AD, Alvir JM, Lieberman JA. Incidence and correlates of acute extrapyramidal symptoms in first episode of schizophrenia. *Psychopharmacol Bull* 1992; 28(1):81-86.

(193) Chatterjee A, Chakos M, Koreen A, Geisler S, Sheitman B, Woerner M et al. Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. *Am J Psychiatry* 1995; 152(12):1724-1729.

(194) Honer WG, Kopala LC, Rabinowitz J. Extrapyramidal symptoms and signs in first-episode, antipsychotic exposed and non-exposed patients with schizophrenia or related psychotic illness. *J Psychopharmacol* 2005; 19(3):277-285.

(195) McCreadie RG, Srinivasan TN, Padmavati R, Thara R. Extrapyramidal symptoms in unmedicated schizophrenia. *J Psychiatr Res* 2005; 39(3):261-266.

(196) Kamis D, Stratton L, Calvo M, Padilla E, Florenzano N, Guerrero G et al. Sex and laterality differences in parkinsonian impairment and transcranial ultrasound in never-treated schizophrenics and their first degree relatives in an Andean population. *Schizophr Res* 2015; 164(1-3):250-255.

(197) Molina JL, Gonzalez AG, Florenzano N, Padilla E, Calvo M, Guerrero G et al. Prediction of Neurocognitive Deficits by Parkinsonian Motor Impairment in Schizophrenia: A Study in Neuroleptic-Naive Subjects, Unaffected First-Degree Relatives and Healthy Controls From an Indigenous Population. *Schizophr Bull* 2016; 42(6):1486-1495.

(198) Janno S, Holi MM, Tuisku K, Wahlbeck K. Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenia population. *BMC Neurol* 2005; 5(1):5.

(199) Knol W, Keijsers CJ, Jansen PA, Belitser SV, Schobben AF, Egberts AC et al. Validity and reliability of the Simpson-Angus Scale (SAS) in drug induced parkinsonism in the elderly. *International journal of geriatric psychiatry* 2009; 24(2).

(200) Calvo-Gomez JM, Sanchez-Pedraza R, Jaramillo-Gonzalez LE, Tarcisio-Mantilla C. [Validating the Simpson-Angus Extrapyramidal Collateral Symptom Evaluation Scale]. *Rev Salud Publica (Bogota)* 2006; 8(1):74-87.

(201) Fervaha G, Agid O, Takeuchi H, Lee J, Foussias G, Zakzanis KK et al. Extrapyramidal symptoms and cognitive test performance in patients with schizophrenia. *Schizophr Res* 2015; 161(2-3):351-356.

(202) Tomita Y, Shichida K, Takeshita K, Takashima S. Maturation of blink reflex in children. *Brain Dev* 1989; 11(6):389-393.

(203) Pearce JM. Observations on the blink reflex. *Eur Neurol* 2008; 59(3-4):221-223.

(204) Friedman JH, Abrantes AM. The glabellar reflex is a poor measure of Parkinson motor severity. *Int J Neurosci* 2013; 123(6):417-419.

(205) Sanchez R, Calvo JM, Jaramillo LE. [Is the glabellar reflex a component of neuroleptic-induced Parkinsonism?]. *Biomedica* 2005; 25(4):539-546.

(206) Azure Kinect DK - Develop AI Models; Microsoft Azure. azure.microsoft.com . 23-3-2019.
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Measuring movements in adolescents with psychosis using the Microsoft Kinect sensor: a pilot study exploring a new tool for assessing aspects of antipsychotic-induced parkinsonism

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Background: The assessment of motor disturbances in antipsychotic-treated adolescent patients is often limited to the use of observer-based rating scales with interobserver variability. The objectives of this pilot study were to measure movement patterns associated with antipsychotic-induced parkinsonism in young patients with psychosis and initiating/treated with antipsychotics, using a computer application connected with the Microsoft Kinect sensor (*Motorgame*). **Method:** All participants were assessed by neurological examination, clinical side effect rating scales (Udvalg for Kliniske Undersøgelser Side Effect Rating Scale, Barnes Akathisia Rating Scale, Simpson Angus Scale (SAS), and Abnormal Involuntary Movement Scale), and the *Motorgame*. Furthermore, speed of information processing and motor speed with subtests from the Brief Assessment of Cognition in Schizophrenia test battery was assessed. **Results:** We included 21 adolescents with first-episode psychosis (62% treated with antipsychotics; males 38%; mean age 16 $\pm$ 1.4 years) and 69 healthy controls (males 36%; mean age 16 $\pm$ 1.5 years). Prolonged time of motor performance (TOMP) in the *Motorgame* was associated with higher SAS scores for arm dropping ($p = .009$). A consistent practice effect was detected ($p < .001$). We found no significant associations between TOMP and age, height, body weight, sex, antipsychotic dosage, or information processing speed. **Conclusions:** We found an uncorrected significant association between prolonged TOMP and shoulder bradykinesia. The *Motorgame* was found useful in assessing parkinsonian symptoms in early-onset psychosis and accepted by participants. Future studies of larger cohorts, including patients with high scores in clinical motor side effect scales, are required to establish solid validity of the novel test.

Key Practitioner Message

- *What's known*: Antipsychotic side effects are often evaluated with observer-based clinical rating scales prone to interobserver variability. Early and objective detection of antipsychotic-induced motor side effect, especially in the young population, is of pivotal importance.
- *What's new*: We found an uncorrected statistically significant association between prolonged time of motor performance and bradykinesia in the shoulders of the participants. The *Motorgame* was found useful and reported as being easy and fun to use by participants.
- *Relevance to clinical practice in child and adolescent mental health*: The Microsoft Kinect sensor has the advantages of being assessable, portable, and of low-cost and holds the potential to become a new quantitative tool for assessing antipsychotic-induced parkinsonism. Future studies of larger cohorts are required to establish solid validity of the test.

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Introduction

Compared to adults, children and adolescents are more prone to develop antipsychotic-induced extrapyramidal symptoms (EPS), that is, akathisia, dystonia, parkinsonism, and dyskinesia (Correll, 2008b). A meta-analysis of 41 controlled short-term studies, including 4015 children and adolescents, of efficacy and safety of second-generation antipsychotics (SGAs) showed that all SGAs, except for quetiapine, significantly increased the risk of EPS compared with placebo: ziprasidone odds ratio (OR) [95% confidence interval (CI)] 20.56 (3.53–68.94); olanzapine OR (CI) 6.36 (2.43–13.84); aripiprazole OR (CI) 3.79 (2.17–6.17); risperidone OR (CI) 3.71 (2.18–6.02); and quetiapine OR (CI) 2.54 (0.88–6.07; Cohen, Bonnot, Bodeau, Consoli, & Laurent, 2012). EPS are defined as distressing antipsychotic-induced motor side effects with the potential to reduce the patient's quality of life and subsequently to interfere with the adherence to antipsychotic treatment. EPS have been associated with poorer prognosis in youth with schizophrenia-spectrum disorders (Stentebjerg-Olesen et al., 2013). Furthermore, the absence of EPS has been associated with improved adherence in adults with schizophrenia (Buchanan, 1992). Therefore, the focus on detecting and minimizing motor adverse events during antipsychotic treatment is of great clinical importance.

Clinical assessment of drug-induced movement disorders

In both clinical practice and for research purposes, antipsychotic side effects are primarily evaluated with clinical rating scales. The fact that they are observer-based, make them prone to interobserver variability, and even well-trained investigators may underestimate the incidence (Wolff & O'Driscoll, 1999). Furthermore, several clinical circumstances call for early and objective detection of motor side effect, especially in the young population. Schizophrenia has been associated with anomalous experiences of self-awareness (self-disorders), which sometimes makes the experience of physical presence and contact of others threatening to patients (Nelson, Whitford, Lavoie, & Sass, 2014). Another frequent symptom in schizophrenia is lack of motivation (Messinger et al., 2011). Compared to healthy controls, persons with schizophrenia perceive themselves as less motivated and specifically report lower situational motivation (the motivation participants experience when they are engaging in an activity; Trémeau, Goldman, Antonius, & Javitt, 2013). Lastly, antipsychotic-induced bradykinesia, especially in its early phases, is difficult to differentiate due to its phenotypic overlap with negative symptoms in schizophrenia and with depression (Prosser et al., 1987). The present study addresses a significant need for an objective method to assess movement disorders in young patients with schizophrenia or other psychotic diseases treated with antipsychotics.

Other researchers have studied objective, quantitative methods to assess antipsychotic-induced movement disorders in adult patients (Caligiuri & Lohr, 1990; Caligiuri et al., 2010; Koning, Tenback, Kahn, Van Schelven, & Van Harten, 2010; Perry et al., 2009; Putzhammer & Klein, 2006; Walther, Koschorke, Horn, & Strik, 2009). To our knowledge, the use of hand-wrist actigraphy has been implemented in clinical practice at some centers (Walther, Horn, et al., 2009; Walther, Koschorke, et al., 2009; Walther et al., 2010), but no previous studies performing quantitative assessment of antipsychotic-induced movement disorders have been conducted in children and adolescents with psychosis.

Kinect-based quantification of movement patterns

The Microsoft Kinect application (2010) was originally developed for motion recognition in gaming applications (Pham, 2009). The Microsoft Kinect combines a regular color camera with a depth sensor and software based on advanced, marker-free pattern recognition (Bonnechere et al., 2014). The sensor maps the scene, and the software recognizes and continuously monitors joint movements three-dimensionally. Additionally, the Microsoft Kinect has the advantages of being assessable, portable, and of low-cost. The validity of the Kinect sensor has been evaluated in a number of studies of motion recognition, that is, neck angle (Allahyari, Sahraneshin, & Khalkhali, 2016), spatiotemporal aspects of gait (Springer & Yogev, 2016), and postural control (Clark et al., 2012). In children, the Microsoft Kinect sensor has been studied as a tool to classify movements during active video gaming (Rosenberg et al., 2016) in 43 healthy children. The study showed excellent reliability between two clinical investigators and the Kinect Tool for jumps, and moderate reliability for sidesteps. Furthermore, the Kinect software has been studied in the evaluation of upper extremity (UE) movement characteristics in 12 healthy, typically developing adolescents (Rammer, Krzak, Riedel, & Harris, 2014). In this study, key kinematic metrics were identified during a validated method of UE motion and proposed for future study (Rammer et al., 2014). The Kinect sensor was reported easy to use for both investigator and participants (Rammer et al., 2014). Studies of Microsoft Kinect in patients with Parkinson's disease have mainly focused on gait assessment (Cancela, Arredondo, & Hurtado, 2014; Cao et al., 2017; Rocha et al., 2014; Takac et al., 2013; Tupa et al., 2015; Zhao, Bunn, Perron, Shen, & Allison, 2015). However, specific motor symptoms, including the items from the Unified Parkinson's Disease Rating Scale measuring typical movement disorder symptoms, were studied by Galna and colleges (Galna et al., 2014). They concluded that the Microsoft Kinect sensor was able to accurately measure gross spatial characteristics and timing of clinically relevant movements.

The aim of this pilot study was to investigate the Kinect-based instrument (*Motorgame*) in a study population of adolescents with psychosis compared to healthy controls matched on age, sex, and parental education, and to validate the *Motorgame* data against the items of rigidity measured by the Simpson Angus Scale (SAS; measuring antipsychotic drug-induced parkinsonism; Simpson & Angus, 1970).

Methods

Design, participants, and inclusion and exclusion criteria

The patient group for this pilot study was on or about to initiate antipsychotic treatment, aged 12–19 years, in an inpatient or outpatient setting, and fulfilled a broad spectrum of clinical diagnoses of nonorganic, non-drug-induced, young-onset psychoses according to ICD-10 (1992) The control group consisted of physically and mentally healthy children and adolescents who completed screening via the Kiddie Schedule for Affective Disorders and Schizophrenia Present Lifetime (K-SADS-PL; a semistructured interview screening for present and previous psychiatric symptoms and disorder; Kaufman et al., 1997), standard somatic history, and clinical examination.

Recruitment. Patients were recruited partly from clinics at the Centre for Child and Adolescent Mental Health, Mental Health Services (CAMHS), Capital Region of Denmark and partly through the Danish multicentre Tolerability and Efficacy of Antipsychotics (TEA) trial (Pagsberg et al., 2014). Healthy controls were part of the TEA trial in which recruitment for controls was performed through a random data extraction from the Danish Centralized Civil Register. The protocol of the present study was submitted to the Committees on Health Research Ethics for the Capital Region of Denmark and the Danish Health Authority, which stated that the study did not require mandatory notification. The Danish Data Protection Agency (DDPA) journal number 2007-58-0015 approved data collecting and data storing. Approval for exchange of information with the TEA trial was given by the DDPA journal number 2013-331-0479. A surrogate written informed consent was obtained from the holders of custody, since all the participants were below the age of 18 years. A small group of the patients engaged in the TEA trial turned 18 years during the study participation and signed an independent written informed consent.

Setting and instrument

This pilot study tested the Kinect-based instrument in an inpatient and outpatient environment. The Kinect application was connected to a computer with the Microsoft game-like software modified by the Technical University of Denmark (DTU) installed (Einarson et al., 2018). The participant was placed at a distance of approximately two meters in front of the computer (Figure 1). A stickman figure that mirrored the participant's movements was visible on the screen. The *Motorgame* consisted of three levels: The participant had to place his/her hand 'on' a stationary spot shown on the screen (level 1: 11 times with the right hand and then 11 times with the left hand), on two spots simultaneously (level 2: 21 times with both hands) and on a moving spot following it slowly in a semicircle either upwards or downwards with both hands taking turns (level 3: 6 times with the right hand and 6 times with the left hand). The *Motorgame* was run twice, that is, the first session as a 'practice run' with instructions given and with the possibility to ask questions and the second session with no instructions. As a motivational factor, points for accuracy and speed were given and shown on screen during the task. Data presented in this paper are exclusively from the second session of level 1. The second session was chosen to ensure that the participants had fully understood the instructions. In addition, data from all three levels were collected, but only data from level 1 were fully analyzed and presented in this paper, since data from level 2 and level 3 showed high levels of variance. Level 2 turned out to require high degree of eye-hand coordination, and the majority of patients had difficulties following the moving spots in level 3. The complexity of the data from level 2 and 3 would have required a more complex statistical modeling with more parameters, accounting for interactions between length of movement in the separate hands, and a bigger sample size to draw any meaningful conclusions.

Figure 1. Kinect assessment

Procedures and outcomes

Demographic and clinical data. We obtained information on sex, age, height, weight, handedness, former/current mental/physical illness, parental educational level, duration of illness, and status of pharmacological treatment through an interview and clinical examination. We collected information according to clinical verified diagnosis of psychosis from medical records.

Assessments. Data collection was carried out from February 2014 to July 2016. All participants were assessed with clinical, cognitive, and neurological examinations. Assessment with the clinical side effect rating scales included the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976; a 12-item rating scale assessing involuntary movements/dyskinesia in various parts of the body with scores ranging from 0 (none) to 4 (severe)), the SAS (SAS; Simpson & Angus, 1970); a 10-item rating scale assessing drug-induced parkinsonism with scores ranging from 0 (none) to 4 (severe), the Barnes Akathisia Rating Scale (BARS; Barnes, 1989); a 4-item scale assessing objective akathisia, subjective awareness of restlessness, subjective distress related to restlessness, and a global akathisia score ranging from 0 (none) to 5 (severe), and the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde, Ahlfors, Bech, Dencker, & Elgen, 1987; assessing antipsychotic-induced side effects in several domains, including movement disorders with scores ranging from 0 (none) to 3 (severe). Additional speed of information processing (Symbol Coding Task measuring the number of correct numerals written in 90 s, ranging from 0 to 110) and motor speed (Token Motor Task measuring the number of tokens correctly placed into the container in 60 s, ranging from 0 to 100), that is, two subtests from Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) was assessed. Finally, two sessions of the *Motorgame* were run. A subgroup of the participants (the patients recruited directly from the clinics at the CAMHS, Capital Region of Denmark) filled out a questionnaire on their opinion of the *Motorgame* compared with the clinical examination from the rating scales and the two subtests from BACS.

All healthy controls and antipsychotic-naive patients recruited directly from the CAMHS were assessed at week 0 and at week 12. The patients on ongoing antipsychotic treatment recruited from the TEA trial were assessed at one of their follow-up time points (predefined in the TEA trial protocol, i.e., weeks 2, 4, 12, and/or 52 after randomization to aripiprazole or quetiapine-ER) and reassessed 12 weeks later.

BACS tests were administered by trained assessors (medical doctors, medical students, and academical staff) after systematic training by two post-doc-level neuropsychologists (BF and JRMJ). The BACS training procedure (Pagsberg et al., 2017) was delineated in agreement with Dr. Richard Keefe from NeuroCog Trials. All assessors were trained in the use of the *Motorgame* by a medical doctor (DR).

Data analysis

Kinect data. The Kinect application tracks the 3D joint positions in the upper body (the hands, wrists, elbows, shoulders, neck, and head) with recordings of 30 times per second. One Kinect *Motorgame* session takes about 5 min and around 9000 3D observations are collected for each joint (Einarson et al., 2018). These data are time series of varying length.

Hypotheses.

1 Higher scores in rigidity (SAS) are associated with prolonged time of motor performance in the *Motorgame*.
2 Higher scores, that is, faster speed of information processing (Symbol Coding Task), are associated with shortened time of motor performance in the *Motorgame*.
3 Practice effects, that is, faster play-through at week 12 compared to week 0, will be present in this young patient and the healthy control group.

Statistics. Descriptive analyses and simple group comparisons were analyzed using Pearson chi-square tests for categorical variables and independent t-test for continuous variables (SPSS version 22+23). Two-sided tests with an uncorrected alpha = 0.05 were used for this exploratory pilot study.

For the statistical analysis of data from the *Motorgame*, we used a linear mixed-effects model (Kuznetsova et al., 2013; McLean et al., 1991) implemented in the package lmer (Kuznetsova et al., 2013) for the R-programming language (R Core Team, 2014). This model contains both a fixed effect and random effects.

The model used:

$$\log(y_{ij}) = \mu + T_j + Cx_{ijC} + Gx_{ijG} + Hx_{ijH} + Ax_{ijA} + Wx_{ijW} + Sx_{ijS} + Lx_{ijL} + \varepsilon_i + \varepsilon_{ij}$$

The terms in the model are y the response (time in s to finish a single task in level 1), μ as a general mean, T_j mean for each of the 22 tasks in level 1, C parameter for the clinical score, where x_{ijC} is the value for that measurements on individual i in task j. G is gender, H the height, W the weight, S the Symbol coding score, and L the learning effect. The last two terms are ε_i, the random effect for individuals and the general error term.

Results

Descriptive data

Twenty-one children and adolescents with psychosis treated with antipsychotics and 69 healthy controls were studied (Table 1). Altogether, 38.1% in the patient group versus 36.2% in the group of healthy controls were male ($p = .877$). Mean age [±standard deviation (*SD*)] was 16.02 ± 1.37 years in the patient and 16.04 ± 1.52 years in the healthy control group ($p = .960$). Parental education level was significantly higher in the healthy control (7.35 ± 0.76) vs. the patient group (6.25 ± 1.33; $p = .002$). Diagnoses included schizophrenia-spectrum disorders (57.1%), affective psychosis (14.4%), and other psychosis (28.5%). The median duration of untreated psychosis (IQR) was 110 days (24.0–301.5 days). Thirteen of the 21 patients had already initiated antipsychotic medication at first assessment with a median duration (IQR) of 4 weeks (0.0–56.5 weeks). Eleven patients were on aripiprazole, 10 on quetiapine IR or ER and one on haloperidol. Antipsychotic doses and comedications are shown in Table 1. Eight patients were antipsychotic-naive at the time of testing at week 0 and initiated the antipsychotic treatment on the same day. However, two antipsychotic-naive patients were excluded at follow-up at week 12 because they had not initiated antipsychotic treatment as planned by their psychiatrist. Dropout rates were high. Ten patients (47.6%) and 19 (27.5%) healthy controls from the TEA trial were lost to follow-up.

Clinical rating scale scores

Clinical rating scale scores of neuromotor symptoms are shown in Table 2. Overall, the clinical rating scale scores of EPS were higher for patients than for healthy controls, but only at a significant level when comparing the SAS scores of the antipsychotic-medicated patients ($n = 9$) with the healthy controls ($n = 50$; $p = .048$). In general, the severity displayed in the clinical rating scales of EPS was predominantly mild, and in a few cases moderate. No participants had dystonia or dyskinesia. Antipsychotic-naive patients ($n = 8$) performed significantly worse in the Token Motor Task (45.4 ± 18.5 point; $p < .001$) and in the Symbol Coding Task (55.1 ± 17.3 points; $p = .016$) compared to the healthy controls ($n = 69$; 67.9 ± 15.1 points and 66.4 ± 11.6 points, respectively). These differences remained significant after the initiation of antipsychotic medication. Changes over time (from week 0 to week 12) are shown in Table 3. No significant between-group differences in changes over time were found ($p = .11$–$.83$).

Mixed models analysis of the Motorgame data

All participants completed the *Motorgame*. The results from the mixed-effects model are shown in Table 4. Arm dropping (item 2 in the SAS) had a statistically significant positive effect on the time of performance in the *Motorgame* (estimate ± *SD* 0.0680 ± 0.0261; $p = .009$), that is, prolonged time of motor performance was associated with higher scores of arm dropping, not correcting for multiple comparisons. Given the 10 tests in the SAS rating scale, arm dropping would not have survived a Bonferroni correction (corrected p-value < .005). Surprisingly, glabellar tap (item 8 in the SAS) had a significant negative effect on the time of performance in the *Motorgame* (estimate ± *SD* −0.0189 ± 0.0056; $p < .001$), that is, shortened time of motor performance was associated with higher scores of glabellar tap. The remaining eight SAS ratings were nonsignificant (p-value range = .138–.919). We did not find any significantly moderating effect of sex, age, height, weight, or antipsychotic dosage. Overall, Symbol Coding Task score had a negative moderating effect on the time of performance in the *Motorgame*, but only at a significant level ($p < .05$) when testing for arm dropping, shoulder shaking, and glabellar tap. A consistent and significant practice effect was observed in the Kinect Motor data (estimate ± *SD* −0.0253 ± 0.0062 to −0.0294 ± 0.0061; $p < .001$; Table 4). Finally, the patient group had a nonsignificant longer performance time in the *Motorgame* (estimate ± *SD* 0.0003 ± 0.0204; $p = .990$) compared to healthy controls.

Questionnaire data

Data from the questionnaire ($n = 8$; Figure 2) showed that 88% found it easy or very easy to understand how to use the *Motorgame*. Moreover, 75% found the *Motorgame* fun or very fun to use. The *Motorgame* was the preferred

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Table 1. Demographic, psychopathologic characteristics, and antipsychotic treatment

	Kinect assessment week 0 (all participants)					Kinect assessment week 0 (participants with week 12 data)			
	Antipsychotic-naive patients *n* = 8	Antipsychotic-medicated patients *n* = 13	Total group of patients *n* = 21	Healthy controls *n* = 69	*p* Value, patients versus healthy controls	Antipsychotic-naive patients *n* = 6	Antipsychotic-medicated patients *n* = 3	Total group of patient *n* = 9	Healthy control *n* = 50
Age in years (range 13.58–19.08), mean ± *SD*	15.5 ± 1.13	16.3 ± 1.46	16.0 ± 1.37	16.0 ± 1.52	.960[a]	15.0 ± 1.10	14.7 ± 1.53	14.9 ± 1.17	14.9 ± 1.42
Male, *n* (%)	4 (50.0)	4 (30.8)	8 (38.1)	25 (36.2)	.877[b]	4 (66.7)	1 (33.3)	5 (55.6)	14 (28.0)
Parental education, mean ± *SD*	5.7 ± 1.38	6.5 ± 1.27	6.3 ± 1.33	7.4 ± 0.76	**.002**[a]	6.0 ± 1.41	6.7 ± 0.58	6.3 ± 1.17	7.2 ± 0.74
Psychosis diagnoses, *n* (%)									
F20.0 Paranoid schizophrenia	9 (69.2)	3 (37.5)	12 (57.1)			3 (50.0)	2 (66.7)	4 (44.4)	
F21.9 Schizotypal personality disorder UNS	0 (0.0)	2 (25.0)	2 (9.5)			1 (16.7)	0 (0.0)	1 (11.1)	
F23.9 Acute and transient psychotic disorder UNS	1 (7.7)	0 (0.0)	1 (4.8)			0 (0.0)	0 (0.0)	0 (0.0)	
F25.1 Schizoaffective disorders, depressive type	1 (7.7)	0 (0.0)	1 (4.8)			0 (0.0)	1 (33.3)	1 (11.1)	
F28.9 Other nonorganic psychosis	0 (0.0)	1 (12.5)	1 (4.8)			1 (16.7)	0 (0.0)	1 (11.1)	
F29.9 Nonorganic psychosis UNS	0 (0.0)	2 (25.0)	2 (9.5)			1 (16.7)	0 (0.0)	1 (11.1)	
F32.3 Severe depressive episode with psychotic symptoms	1 (7.7)	0 (0.0)	1 (4.8)			0 (0.0)	0 (0.0)	0 (0.0)	
F33.3 3 Recurrent depressive episode, current episode severe with psychotic symptoms.	1 (7.7)	0 (0.0)	1 (4.8)			0 (0.0)	0 (0.0)	0 (0.0)	
Psychiatric comorbid diagnosis, n (%)	4 (50.0)	7 (53.8)	11 (52.4)			3 (50.0)	0 (0.0)	3 (33.3)	
Duration of untreated psychosis, median weeks (IQR)	180.0 (48.0–624.0)	55.0 (22.0–220.0)	110.0 (24.0–301.5)						
Antipsychotic									
Aripiprazole, n (%)	0 (0.0)	6 (46.2)	11 (52.4)			0 (0.0)	2 (66.6)	2 (22.2)	
Aripiprazole, median dose, mg (range)	–	15.0 (15.0–20.0)	15.0 (15–20.0)			–	17.5 (15.0–20.0)	17.5 (15–20.0)	

(continued)

Table 1. (continued)

	Kinect assessment week 0 (all participants)					Kinect assessment week 0 (participants with week 12 data)			
	Antipsychotic-naive patients *n* = 8	Antipsychotic-medicated patients *n* = 13	Total group of patients *n* = 21	Healthy controls *n* = 69	*p* Value, patients versus healthy controls	Antipsychotic-naive patients *n* = 6	Antipsychotic-medicated patients *n* = 3	Total group of patient *n* = 9	Healthy control *n* = 50
Quetiapine, *n* (%)	0 (0.0)	3 (23.1)	5 (23.8)			0 (0.0)	0 (0.0)	0 (0.0)	
Quetiapine, median dose, mg (range)	–	200.0 (20.0–400.0)	200.0 (20.0–400.0)			–	–	–	
Quetiapine-ER, *n* (%)	0 (0.0)	5 (38.5)	5 (23.8)			0 (0.0)	1 (33.3)	1 (11.1)	
Quetiapine-ER, median dose, mg (range)	–	600.0 (100.0–600.0)	600.0 (100.0–600.0)			–	200.0 (200.0–200.0)	200.0 (200.0–200.0)	
Haloperidol, *n* (%)	0 (0.0)	1 (7.7)	1 (4.8)			0 (0.0)	0 (0.0)	0 (0.0)	
Haloperidol, median dose, mg (range)	–	2 (2.0–2.0)	2 (2.0–2.0)			–	–	–	
Paliperidone, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)			0 (0.0)	0 (0.0)	0 (0.0)	
Paliperidone, median monthly dose, mg (range)	–	–	–			–	–	–	
Duration of antipsychotic treatment at first assessment, median weeks (range)	0 (0–0)	56.0 (8.0–60.0)	4 (8.0–60.0)						
Antidepressant									
Sertraline, *n* (%)	0	1 (7.7)	1 (4.8)			0 (0.0)	0 (0.0)	0 (0.0)	
Sertraline, median dose, mg (range)	–	50 (50.0–50.0)	50 (50.0–50.0)			–	–	–	
Fluoxetine, *n* (%)	0	2 (15.4)	2 (9.5)			0 (0.0)	1 (33.3)	1 (11.1)	
Fluoxetine, median dose, mg (range)	–	20 (20.0–20.0)	20 (20.0–20.0)			–	20 (20.0–20.0)	20 (20.0–20.0)	
Mood stabilizers	–	–	–	–	–	–	–	–	
Anxiolytic/hypnotic									
Oxapax pronecessitate, *n* (%)	1 (12.5)	0	1 (4.8)			0 (0.0)	0 (0.0)	0 (0.0)	
Oxapax, median dose, mg (range)	15 (15.0–15.0)	–	15 (15.0–15.0)			–	–	–	
Lorazepam, *n* (%)	0	1 (7.7)	1 (4.8)			0 (0.0)	0 (0.0)	0 (0.0)	
Lorazepam, median dose, mg (range)	–	0.5 (0.5–0.5)	0.5 (0.5–0.5)			–	–	–	
Anticholinergics									
Lysantin, *n* (%)	0	2 (15.4)	2 (9.5)			0 (0.0)	0 (0.0)	0 (0.0)	

(continued)

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Table 1. (continued)

	Kinect assessment week 0 (all participants)					Kinect assessment week 0 (participants with week 12 data)			
	Antipsychotic-naive patients *n* = 8	Antipsychotic-medicated patients *n* = 13	Total group of patients *n* = 21	Healthy controls *n* = 69	*p* Value, patients versus healthy controls	Antipsychotic-naive patients *n* = 6	Antipsychotic-medicated patients *n* = 3	Total group of patient *n* = 9	Healthy control *n* = 50
Lysantin pro necessitate, median dose, mg (range)	–	50.0 (50.0–50.0)	50.0 (50.0–50.0)			–	–	–	
Akineton, *n* (%)	0	2 (15.2)	2 (9.5)			0 (0.0)	0 (0.0)	0 (0.0)	
Akineton, median dose, mg (range)	–	1.5 (1.0–2.0)	1.5 (1.0–2.0)			–	–	–	

	Kinect assessment week 12				Group comparisons in participants with week 0 and week 12 data		
	Antipsychotic-naive patient *n* = 6	Antipsychotic-medicated patients *n* = 3	Total group of patient *n* = 9	Healthy controls *n* = 50	*p* Value, patients versus healthy controls	*p* Value, patients week 0 versus week 12	*p* Value, healthy controls week 0 versus week 12
Age in years (range 13.58–19.08), mean ± *SD*	15.0 ± 1.10	14.7 ± 1.53	14.9 ± 1.17	14.9 ± 1.42	.982[a]	.122[a]	.647[a]
Male, *n* (%)	4 (66.7)	1 (33.3)	5 (55.6)	14 (28.0)	.103[b]	.600[b]	.349[b]
Parental education, mean ± *SD*	6.0 ± 1.41	6.7 ± 0.58	6.3 ± 1.17	7.2 ± 0.74	**.052**[a]	.647[a]	.362[a]
Psychosis diagnoses, *n* (%)							
F20.0 Paranoid schizophrenia	3 (50.0)	2 (66.7)	4 (44.4)				
F21.9 Schizotypal personality disorder UNS	1 (16.7)	0 (0.0)	1 (11.1)				
F23.9 Acute and transient psychotic disorder UNS	0 (0.0)	0 (0.0)	0 (0.0)				
F25.1 Schizoaffective disorders, depressive type	0 (0.0)	1 (33.3)	1 (11.1)				
F28.9 Other nonorganic psychosis	1 (16.7)	0 (0.0)	1 (11.1)				
F29.9 Nonorganic psychosis UNS	1 (16.7)	0 (0.0)	1 (11.1)				
F32.3 Severe depressive episode with psychotic symptoms	0 (0.0)	0 (0.0)	0 (0.0)				
F33.3 3 Recurrent depressive episode, current episode severe with psychotic symptoms.	0 (0.0)	0 (0.0)	0 (0.0)				
Psychiatric comorbid diagnosis, n (%)	3 (50.0)	0 (0.0)	3 (33.3)				
Duration of untreated psychosis, median weeks (IQR)							
Antipsychotic							
Aripiprazole, n (%)	5 (83.3)	1 (33.3)	6 (28.6)				
Aripiprazole, median dose, mg (range)	5.0 (2.5–10)	30.0 (30.0–30.0)	7.5 (2.5–30)				
Quetiapine, *n* (%)	2 (33.3)	0 (0.0)	2 (22.2)				
Quetiapine, median dose, mg (range)	212.5 (25.0–400.0)	0 (0.0)	212.5 (25.0–400.0)				
Quetiapine-ER, *n* (%)	0 (0.0)	1 (33.3)	1 (11.1)				

(continued)

Table 1. (continued)

	Kinect assessment week 12				Group comparisons in participants with week 0 and week 12 data		
	Antipsychotic-naive patient *n* = 6	Antipsychotic-medicated patients *n* = 3	Total group of patient *n* = 9	Healthy controls *n* = 50	*p* Value, patients versus healthy controls	*p* Value, patients week 0 versus week 12	*p* Value, healthy controls week 0 versus week 12
Quetiapine-ER, median dose, mg (range)	–	400.0 (400.0–400.0)	400.0 (400.0–400.0)				
Haloperidol, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)				
Haloperidol, median dose, mg (range)	–	–	–				
Paliperidone, *n* (%)	0 (0.0)	1 (33.3)	1 (11.1)				
Paliperidone, median monthly dose, mg (range)	–	75.0 (75.0–75.0)	75.0 (75.0–75.0)				
Duration of antipsychotic treatment at first assessment, median weeks (range)							
Antidepressant							
Sertraline, *n* (%)	0	0	0				
Sertraline, median dose, mg (range)	–	–	–				
Fluoxetine, *n* (%)	0	1 (33.3)	1 (11.1)				
Fluoxetine, median dose, mg (range)		20 (20.0–20.0)	20 (20.0–20.0)				
Mood stabilizers	–	–	–	–	–		
Anxiolytic/hypnotic							
Oxapax pronecessitate, *n* (%)	2 (33.3)	0	2 (22.2)				
Oxapax, median dose, mg (range)	11.3 (7.5–15)	–	11.3 (7.5–15)				
Lorazepam, *n* (%)	0	0	0				
Lorazepam, median dose, mg (range)	–	–	–				
Anticholinergics							
Lysantin, *n* (%)	0	0	0				
Lysantin pro necessitate, median dose, mg (range)	–	–	–				
Akineton, *n* (%)	0	0	0				
Akineton, median dose, mg (range)	–	–	–				

IQR, interquartile range; *SD*, standard deviation.
[a]Independent *t*-test.
[b]Pearson chi-square test.
Significant *p* values are in bold.

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Table 2. Scores on clinical rating scales (UKU, SAS, BARS, AIMS/tardive dyskinesia) and performance tests (Token Motor Task and Symbol Coding Task)

	Antipsychotic-naive patients (ANP)		Antipsychotic-medicated patients (AMP)		Healthy controls (HC)		*p* Value patients versus HC (comparison between Kinect assessments week 12)	*p* Value ANP versus AMP (comparison between Kinect assessments week 0)	*p* Value ANP versus HC (comparison between Kinect assessments week 0)
	Kinect assessment week 0, unmedicated, *n* = 8	Kinect assessment week 12, medicated, *n* = 6	Kinect assessment week 0, medicated, *n* = 13	Kinect assessment week 12, medicated, *n* = 3	Kinect assessment week 0, *n* = 69	Kinect assessment week 12, *n* = 50			
Item 2.3 UKU (bradykinesia), range 0–3, mean ± *SD*	0.13 ± 0.35	0.33 ± 0.52	0.08 ± 0.28	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	.169	.732	.351
Mean SAS total score, range 0–0.4 mean ± *SD*	0.09 ± 0.14	0.23 ± 0.22	0.16 ± 0.16	0.13 ± 0.15	0.07 ± 0.14	0.09 ± 0.14	**.048**	.281	.664
BARS global score, range 0–5, mean ± *SD*	0.63 ± 0.74	1.17 ± 1.60	1.00 ± 1.00	0.67 ± 1.16	0.03 ± 0.17	0.02 ± 0.14	.071	.373	.058
Tardive dyskinesia, *n* (%)	0	0	0	0	0	0	–	–	–
Token Motor Task, range 0–100, mean ± *SD*	45.4 ± 18.5	49.0 ± 14.5	47.7 ± 18.5	56.0 ± 14.1	67.9 ± 15.1	75.3 ± 13.7[a]	**<.001**	.789	**<.001**
Symbol Coding Task, range 0–110, mean ± *SD*	55.1 ± 17.3	52.2 ± 17.5	53.0 ± 15.0	64.0 ± 7.1	66.4 ± 11.6	72.7 ± 11.1[a]	**.003**	.774	**.016**

SD, standard deviation; independent *t*-test (including Levene's test for equality of variances) used for comparison.
[a]Only 20 healthy participants were assessed regarding Token Motor Task and Symbol Coding Task at second Kinect assessment.
Significant *p* values are in bold.

Table 3. Changes over time (from week 0 to week 12) in clinical rating scales (UKU, SAS, BARS, AIMS/tardive dyskinesia) and performance tests (Token Motor Task and Symbol Coding Task) of patients with both week 0 and week 12 Kinect assessments

	Antipsychotic-naive patients (ANP), *n* = 6	Antipsychotic-medicated patients (AMP), *n* = 3	Healthy controls (HC), *n* = 50	*p* Value AMP versus HC	*p* Value ANP versus AMP	*p* value ANP versus HC
Change Item 2.3 UKU (bradykinesia), mean ± *SD*	0.167 ± 0.753	−0.333 ± 0.577	0.00 ± 0.0	.423	.351	.611
Change mean SAS total score, mean ± *SD*	0.183 ± 0.214	−0.033 ± 0.321	0.012 ± 0.117	.830	.259	.108
Change BARS global score, mean ± *SD*	0.667 ± 1.633	−0.067 ± 0.577	−0.020 ± 0.247	.191	.224	.351
Change Token Motor Task, mean ± *SD*	3.17 ± 20.81	8.00 ± 5.66	5.25 ± 17.76	.833	.768	.810
Change Symbol Coding Task, mean ± *SD*	−3.5 ± 18.89	0.00 ± 9.90	3.00 ± 7.41	.598	.817	.444

Independent *t*-test (including Levene's test for equality of variances) used for comparison. *SD*, standard deviation.

test by 37.5%, but exceeded by the BACS tests (Token Motor Task and Symbol Coding Task), which was preferred by 62.5%.

Discussion

Antipsychotics have been used increasingly in children and adolescents, both for psychotics and nonpsychotic mental disorders (Olfson, 2009; Olfson, Blanco, Liu, Moreno, & Laje, 2006; Olfson, Blanco, Liu, Wang, & Correll, 2012; Olfson, Crystal, Huang, & Gerhard, 2010). Children and adolescents are more likely to experience EPS during antipsychotic treatment compared to adults (Correll, 2008a).

With the present study, we wanted to identify differences in movement patterns between young patients with psychosis and healthy controls and validate the *Motorgame* data against data from the established clinical side effect rating scales. We expectedly found a significant difference in the mean SAS total score between antipsychotic-medicated patients and healthy controls. Motor speed (Token Motor Task) was significantly lower in both antipsychotic-unmedicated and antipsychotic-medicated patients compared to the group of healthy controls. Parkinsonism has previously been solidly documented in antipsychotic-naive patients with first-episode schizophrenia and in their at-risk, but unaffected, first-degree relatives (Caligiuri, Lohr, & Jeste, 1993; Chakos, Mayerhoff, Loebel, Alvir, & Lieberman, 1992; Chatterjee et al., 1995; Honer, Kopala, & Rabinowitz, 2005; McCreadie, Srinivasan, Padmavati, & Thara, 2005) with highest severity in affected patients, intermediate severity in unaffected relatives, and nearly absent parkinsonian motor impairment in healthy controls (Kamis et al., 2015; Molina et al., 2016). In addition, we found that speed of information processing (Symbol Coding Task) was significantly lower in both antipsychotic-unmedicated and antipsychotic-medicated patients compared to the group of healthy controls. This is in line with previous findings from a study of reliability, sensitivity, and validity of BACS comparing 150 adult patients with schizophrenia and 50 healthy controls (Keefe et al., 2004).

In the linear mixed models analysis, we found that arm dropping (item 2) in the SAS rating scale had the largest and a significant effect uncorrected for multiple comparisons on the time of motor performance in the *Motorgame*. Since none of the other five closely related SAS rigidity items (shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, or head dropping) displayed significant effects, this finding may have been due to a type I error due to small sample size and multiple testing. However, we can also not rule out that the nonsignificant results were due to a type II error, also related to the small sample size. Validation and reliability studies of the Simpson Angus scale have previously demonstrated good internal consistency with Cronbach's alpha coefficients of 0.79–0.93 (Janno, Holi, Tuisku, & Wahlbeck, 2005; Knol et al., 2009; Calvo-Gomez, Sanchez-Pedraza, Jaramillo-Gonzalez, & Tarcisio-Mantilla, 2006). However, the Microsoft Kinect sensor has previously been studied and validated against a Vicon three-dimensional motion analysis system in nine patients with Parkinson's disease and 10 controls (Galna et al., 2014). Galna and colleges found that the timing of repetitive shoulder and elbow movements based on UPDRS III (Goetz et al., 2008; a validated tool measuring the severity of motor disability in patients with Parkinson's disease) was measured very accurately by the Kinect sensor.

Furthermore, we found a negative significant effect of glabellar tap (item 8) in the SAS. All participants with an abnormal glabellar tap were found in the patient group, except from one healthy control with a score of 1 (mild). The glabellar reflex is one out of many behavioral motor responses found in neonates, which is subsequently inhibited before the age of 5 years (Tomita, Shichida, Takeshita, & Takashima, 1989). An abnormal glabellar reflex is primarily seen in diffuse cerebral hemisphere degenerative and vascular diseases (Pearce, 2008). In a study of patients with Parkinsonian disorders (Parkinson's disease, supranuclear palsy, multiple system atrophy), the glabellar tap showed a modest sensitivity, but a lack of specificity (Brodsky, Dat, Thomas, & Jankovic, 2004). Glabellar tap is in general considered to be nonspecific, nondiagnostic, and a poor measure of

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Table 4. The effect of Simpson Angus Scale items and patient status on the time of motor performance in the Kinect Motorgame

Model	SAS score/ patient status	Gender	Age	Height	Weight	Antipsychotic dosage in chlorpromazine equivalents	Symbol coding task	Repetition
SAS item 1: Gait Parameter value (*SD*)	0.0566 (0.0381)	0.0288 (0.0175)	0.0004 (0.0047)	0.0017 (0.0011)	−0.0010 (0.0007)	−0.0001 (0.0001)	−0.0009 (0.0005)	−0.0294 (0.0061)
p-Value	.138	.104	.939	.130	.184	.053	.093	**<.001**
SAS item 2: Arm dropping Parameter value (*SD*)	0.0680 (0.0261)	0.0304 (0.0171)	0.0003 (0.0046)	0.0014 (0.0011)	−0.0007 (0.0007)	−0.0001 (0.0001)	−0.0010 (0.0005)	−0.0253 (0.0062)
p-Value	**.009**	.079	.956	.191	.290	.066	.044	**<.001**
SAS item 3: Shoulder shaking Parameter value (*SD*)	0.0163 (0.0146)	0.0323 (0.0174)	−0.0002 (0.0047)	0.0016 (0.0011)	−0.0007 (0.0007)	−0.0001 (0.0001)	−0.0010 (0.0005)	−0.0284 (0.0061)
p-Value	.264	.066	.959	.147	.311	.064	**.050**	**<.001**
SAS item 4: Elbow rigidity Parameter value (*SD*)	−0.0015 (0.0149)	0.0300 (0.0174)	−0.0005 (0.0047)	0.0015 (0.0011)	−0.0007 (0.0007)	−0.0001 (0.0001)	−0.0010 (0.0005)	−0.0284 (0.0061)
p-Value	.919	.088	.916	.168	.308	.063	.060	**<.001**
SAS item 5: Wrist rigidity Parameter value (*SD*)	0.0344 (0.0357)	0.0323 (0.0174)	−0.0003 (0.0047)	0.0016 (0.0011)	−0.0007 (0.0007)	−0.0001 (0.0001)	−0.0010 (0.0005)	−0.0280 (0.0061)
p-Value	.335	.066	.951	.156	.313	.063	.051	**<.001**
SAS item 6: Leg pendulousness Parameter value (*SD*)	0.0199 (0.0278)	0.0304 (0.0173)	−0.0002 (0.0047)	0.0015 (0.0011)	−0.0007 (0.0007)	−0.0001 (0.0001)	−0.0010 (0.0005)	−0.0286 (0.0061)
p-Value	.474	.083	.967	.172	.334	.065	.057	**<.001**
SAS item 7: Head dropping Parameter value (*SD*)	−0.0153 (0.0208)	0.0287 (0.0175)	−0.0008 (0.0047)	0.0015 (0.0011)	−0.0007 (0.0007)	−0.0001 (0.0001)	−0.0010 (0.0005)	−0.0287 (0.0061)
p-Value	.462	.104	.873	.170	.296	.062	.061	**<.001**
SAS item 8: Glabellar tap Parameter value (*SD*)	−0.0189 (0.0056)	0.0358 (0.0183)	−0.0005 (0.0049)	0.0017 (0.0012)	−0.0006 (0.0007)	−0.0001 (0.0001)	−0.0013 (0.0005)	−0.0273 (0.0061)
p-Value	**<.001**	.055	.927	.150	.429	.121	**.025**	**<.001**
SAS item 9: Tremor Parameter value (*SD*)	−0.0116 (0.0085)	0.0293 (0.0175)	−0.0006 (0.0047)	0.0015 (0.0011)	−0.0007 (0.0007)	−0.0001 (0.0001)	−0.0010 (0.0005)	−0.0261 (0.0064)
p-Value	.174	.099	.903	.194	.311	.124	.068	**<.001**
SAS item 10: Salivation Parameter value (*SD*)	−0.0088 (0.0214)	0.0299 (0.0173)	−0.0005 (0.0047)	0.0015 (0.0011)	−0.0007 (0.0007)	−0.0001 (0.0001)	−0.0010 (0.0005)	−0.0288 (0.0061)
p-Value	.680	.088	.910	.168	.300	.073	.056	**<.001**
Patient status Parameter value (*SD*)	0.0003 (0.0204)	0.0305 (0.0175)	0.0003 (0.0047)	0.0016 (0.0011)	−0.0008 (0.0007)	−0.0001 (0.0001)	−0.0009 (0.0005)	−0.0261 (0.0061)
p-Value	.990	.085	.954	.166	.263	.203	.092	**<.001**

Mixed models analysis. Results are log-transformed (natural logarithm). Each parameter estimate is presented with the standard deviation (±*SD*).
Significant *p* values are in bold.

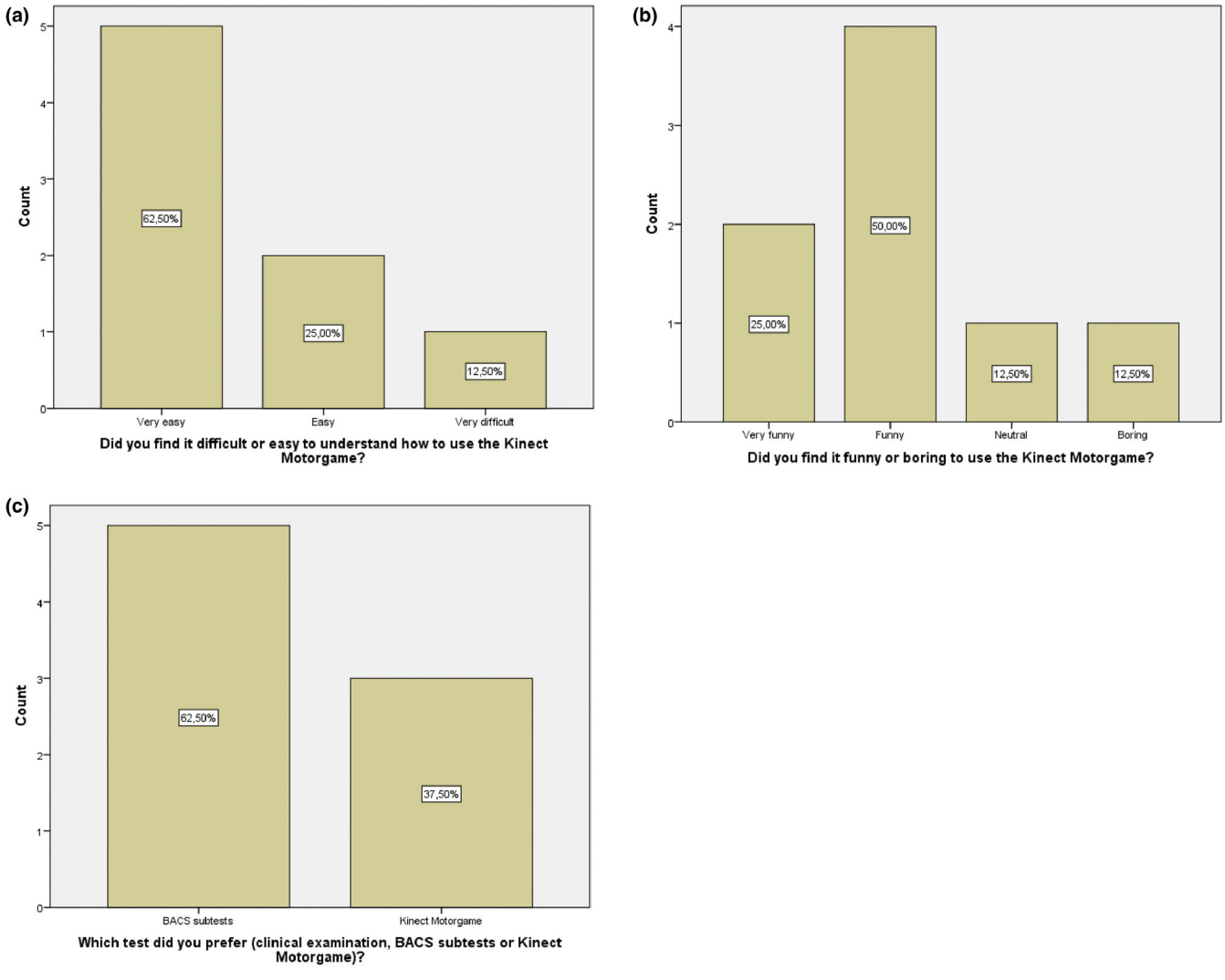

Figure 2. Results from the questionnaire about the participants (n = 8) opinion about the Kinect Motorgame [Colour figure can be viewed at wileyonlinelibrary.com]

Parkinson motor severity, which is the reason why the glabellar tap is no longer used in clinical neurology for the assessment of parkinsonism (Friedman & Abrantes, 2013). In studies of antipsychotic-naive or antipsychotic-free (1–6 months) patients with schizophrenia, an abnormal glabellar tap was found in 40%–77% (Stevens, 1978a, 1978b). Other researchers have found that the glabellar tap item is not correlated to the other items of parkinsonism in the SAS (Calvo-Gomez et al., 2006; Sanchez, Calvo, & Jaramillo, 2005). Our finding is most likely related to a type I error due to the small sample size, since no theoretical reasons or study results would currently support such an association.

We did not find any moderating effect of sex, age, height, weight, or antipsychotic dosage. However, we found a somewhat surprising trend showing a non-significant negative moderating effect of antipsychotic dosage on the time of motor performance (i.e., shortened performance time). Most antipsychotics show a dose-dependent threshold of dopamine D_2 receptor occupancy in the central nervous system for their therapeutic effects, as well as for their extrapyramidal effects (Kapur & Mamo, 2003). However, second-generation antipsychotics show a lower propensity of extrapyramidal symptoms due to faster dissociation from the dopamine D_2 receptor (Kapur & Seeman, 2001). Since this association does not reach the level of significance, this has to be further investigated in future studies of larger cohorts.

We found that speed of information processing (Symbol Coding Task) had a negative moderating effect on the performance in the Motorgame at a significant level ($p < .05$) when tested for arm dropping, shoulder shaking, and glabellar tap in the Simpson Angus Scale. In accordance with our finding, Fervaha and colleagues showed that the severity of parkinsonism (assessed by SAS) was reliably linked with poorer scores on tests of cognition (verbal memory, processing speed, and working memory in nonmedicated adult patients with schizophrenia (Fervaha et al., 2015).

Not surprisingly for this age-group, a consistent and clear practice effect was found in the present study.

In the linear mixed models analysis, we did not find any significant effect of the UKU hypokinesia score, BARS akathisia scores, or AIMS involuntary movement scores on the time of performance in the *Motorgame* (data not shown). Both the patient group, as well as the healthy control group, had very low scores in these rating scales, and differences were hence not possible to detect.

In the present *Motorgame,* we did not find a significant difference in the time used on motor performance between patients and healthy controls. This result might be due to the low proportion of first-episode psychosis patients in the study as well as the fact, that they overall showed a relatively low severity of motor side effects.

The *Motorgame* was reported easy and fun to use and was preferred by patients above all other clinical rating scales used in the present study except for the brief employed BACS subtests. This is in line with previous studies in children and adolescents using the Microsoft Kinect: In a pilot project of physical rehabilitation in young adults with motor disabilities, a Kinect-based instrument showed enhanced motivation among the participants (Chang, Chen, & Huang, 2011). In a study of young patients with hemiplegic cerebral palsy, the authors concluded that Kinect was easy to use and had the potential for improving functional assessment (Rammer et al., 2014). In a crossover study of traditional exercise (a stationary bicycle) and Kinect as an exercise intervention in 30 young subjects with Cystic Fibrosis, participants preferred Xbox Kinect for its interactivity (Salonini et al., 2015).

The strengths of this study were the inclusion of healthy controls and the testing of practice effects, measures relevant for repeated measurements in clinical practice. The equipment used in this study was low-cost, easily accessible, portable, and does not require expert knowledge to use. The similarities of the Kinect-based test to an ordinary computer game and the reduced time of physical contact with the physician are factors that are expected to increase the patient's willingness to participate.

The present study has some limitations. First, the *Motorgame* covered only a part of the clinical examination of EPS, that is, drug-induced parkinsonism. Thus, it remains untested whether the Kinect sensor can measure tremor and dyskinesia. However, this is a limitation within the actual version of the software in the Kinect-based instrument used in the present study, which a newer version might solve. Second, the *Motorgame* covered only upper extremity movements, which means that head and lower extremity movements were not assessed. Third, the level of parkinsonian side effects during the medical treatment with antipsychotics was low, diminishing the power of the analyses. Fourth, information regarding the diagnosis of psychosis was collected from medical records. Diagnoses were routinely assessed through Kiddie Schedule for Affective Disorders and Schizophrenia Present Lifetime (K-SADS-PL; Kaufman et al., 1997) or Present State Examination (short version of Schedules for Clinical Assessment in Neuropsychiatry for clinical use (Wing et al., 1990) by the psychiatrists, but not further verified in the study. Fifth, dropout rates were high, increasing the risk of estimates getting biased, as well as increasing statistical variance and risk of type II errors. Sixth, results were not systematically statistical corrected for multiple testing, increasing the risk of both type 1 and type 2 errors. The Bonferroni correction was used when evaluating the SAS scores. Finally, the number of first-episode psychosis patients in our study was small with 13 patients on antipsychotic medication and eight antipsychotic-naive patients. A larger sample size would have added more power to the study and have reduced the risk of type I errors, since young individuals are less different than adults.

Conclusion

In the present exploratory pilot study, using the newly developed Kinect-based algorithm (*Motorgame*), we found a statistically significant association between prolonged time of performance in the *Motorgame* and SAS arm dropping in the participants when using uncorrected *p*-values. Surprisingly, a shortened time of motor performance was associated with higher scores of glabellar tap. As expected in this young population, we detected a consistent practice effect in the *Motorgame*, which has to be studied and accounted for in future longitudinal studies. In conclusion, the *Motorgame* was found useful, and accepted by participants for the assessment of parkinsonian symptoms in early-onset psychosis and holds the potential for improving the clinical assessment of antipsychotic-induced parkinsonism in this study population. Future studies of larger cohorts, including patients with higher degrees of motor side effect severity, are required to establish solid validity of the test.

Clinical significance

This exploratory pilot study is a methodological development study. The results need to be further evaluated in future studies in order to increase our knowledge, particularly about what characterizes the movements of patients with higher clinical motor side effect scale scores. Further development and studies of better sensors are needed to improve tracking of tremor (possibly by including newer versions of the software). Future validation studies and a randomized control trial are mandatory before the *Motorgame* can be used in the clinics as a diagnostic tool. An objective and contactless instrument for movement disorder might also be relevant to other patient groups in child and adolescent psychiatry that are difficult to examine in person, for example, patients with autism spectrum disorders, intellectual disability, and patients suffering from catatonia. This type of technology holds the potential for future for quantitative, repeated, in-hospital measurements, but also for in-home use, allowing the patient to provide automated reports to the neurologist/psychiatrist.

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D.R. initiated the study. D.R., G.E.I., J.B.M., C.U.C., D.G.K., J-R.M.J., B.F., K.W.I., R.R.P., A.K.P., and A.F.J. made important contributions to the study conception, design, and protocol. D.R. led the manuscript drafting. D.R., A.K.P., A.F-J., R.R.P., and G.E.I. were involved in drafting. J.B.M., G.E.I., and

R.R.P. have developed the application for the Kinect sensor. D.R. and G.E.I. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. G.E.I. has conducted the mixed models analysis. D.R., K.G.J., C.R.I., A.S.A., and S.K.R. performed the assessments. All authors have critically revised the manuscript and approved submission of the final version.

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Ethical information

The protocol of the present study was submitted to the Committees on Health Research Ethics for the Capital Region of Denmark and the Danish Health Authority, which stated that the study did not require mandatory notification. The Danish Data Protection Agency (DDPA) journal number 2007-58-0015 approved data collecting and data storing. Approval for exchange of information with the TEA trial was given by the DDPA journal number 2013-331-0479.

A surrogate written informed consent was obtained from the holders of custody, since all the participants were below the age of 18 years. A small group of the patients engaged in the TEA trial turned 18 years during the study participation and signed an independent written informed consent.

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References

Allahyari, T., Sahraneshin, S.A., & Khalkhali, H.R. (2016). Validity of the Microsoft Kinect for measurement of neck angle: Comparison with electrogoniometry. *International Journal of Occupational Safety and Ergonomics*, *23*, 524–532.

Barnes, T.R. (1989). A rating scale for drug-induced akathisia. *British Journal of Psychiatry*, *154*, 672–676.

Bonnechere, B., Jansen, B., Salvia, P., Bouzahouene, H., Omelina, L., Moiseev, F., … & Van Sint Jan, S. (2014). Validity and reliability of the Kinect within functional assessment activities: Comparison with standard stereophotogrammetry. *Gait & Posture*, *39*, 593–598.

Brodsky, H., Dat, V.K., Thomas, M., & Jankovic, J. (2004). Glabellar and palmomental reflexes in Parkinsonian disorders. *Neurology*, *63*, 1096–1098.

Buchanan, A. (1992). A two-year prospective study of treatment compliance in patients with schizophrenia. *Psychological Medicine*, *22*, 787–797.

Caligiuri, M.P., & Lohr, J.B. (1990). Fine force instability: A quantitative measure of neuroleptic-induced dyskinesia in the hand. *Journal of Neuropsychiatry and Clinical Neurosciences*, *2*, 395–398.

Caligiuri, M.P., Lohr, J.B., & Jeste, D.V. (1993). Parkinsonism in neuroleptic-naive schizophrenic patients. *American Journal of Psychiatry*, *150*, 1343–1348.

Caligiuri, M.P., Teulings, H.L., Dean, C.E., Niculescu, A.B., & Lohr, J. B. (2010). Handwriting movement kinematics for quantifying extrapyramidal side effects in patients treated with atypical antipsychotics. *Psychiatry Research*, *177*, 77–83.

Calvo-Gomez, J.M., Sanchez-Pedraza, R., Jaramillo-Gonzalez, L.E., & Tarcisio-Mantilla, C. (2006). Validating the Simpson-Angus Extrapyramidal Collateral Symptom Evaluation Scale. *Revista de salud publica (Bogota, Colombia)*, *8*, 74–87.

Cancela, J., Arredondo, M.T., & Hurtado, O. (2014). Proposal of a Kinect(TM)-based system for gait assessment and rehabilitation in Parkinson's disease. *Conference of the IEEE Engineering in Medicine and Biology Society*, *2014*, 4519–4522.

Cao, Y., Li, B.Z., Li, Q.N., Xie, J.D., Cao, B.Z., & Yu, S.Y. (2017). Kinect-based gait analyses of patients with Parkinson's disease, patients with stroke with hemiplegia, and healthy adults. *CNS Neuroscience & Therapeutics*, *23*, 447–449.

Chakos, M.H., Mayerhoff, D.I., Loebel, A.D., Alvir, J.M., & Lieberman, J.A. (1992). Incidence and correlates of acute extrapyramidal symptoms in first episode of schizophrenia. *Psychopharmacology Bulletin*, *28*, 81–86.

Chang, Y.J., Chen, S.F., & Huang, J.D. (2011). A Kinect-based system for physical rehabilitation: a pilot study for young adults with motor disabilities. *Research in Developmental Disabilities*, *32*, 2566–2570.

Chatterjee, A., Chakos, M., Koreen, A., Geisler, S., Sheitman, B., Woerner, M., … & Lieberman, J.A. (1995). Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. *American Journal of Psychiatry*, *152*, 1724–1729.

Clark, R.A., Pua, Y.H., Fortin, K., Ritchie, C., Webster, K.E., Denehy, L., & Bryant, A.L. (2012). Validity of the Microsoft Kinect for assessment of postural control. *Gait & Posture*, *36*, 372–377.

Cohen, D., Bonnot, O., Bodeau, N., Consoli, A., & Laurent, C. (2012). Adverse effects of second-generation antipsychotics in children and adolescents: A Bayesian meta-analysis. *Journal of Clinical Psychopharmacology*, *32*, 309–316.

Correll, C.U. (2008a). Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 9–20.

Correll, C.U. (2008b). Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents. *Journal of Clinical Psychiatry*, *69*, 26–36.

Einarson, G., Clemmesen, L.K.H., & Rudå, D. (2018). *Computer aided identification of motion disturbances related to Parkinson's Disease* (vol. 11121) International Workshop on PRedictive Intelligence In MEdicine. PRIME 2018. Part of the Lecture Notes in Computer Science book series (LNCS).

Fervaha, G., Agid, O., Takeuchi, H., Lee, J., Foussias, G., Zakzanis, K.K., … & Remington, G. (2015). Extrapyramidal symptoms and cognitive test performance in patients with schizophrenia. *Schizophrenia Research*, *161*, 351–356.

Friedman, J.H., & Abrantes, A.M. (2013). The glabellar reflex is a poor measure of Parkinson motor severity. *International Journal of Neuroscience*, *123*, 417–419.

Galna, B., Barry, G., Jackson, D., Mhiripiri, D., Olivier, P., & Rochester, L. (2014). Accuracy of the Microsoft Kinect sensor for measuring movement in people with Parkinson's disease. *Gait & Posture*, *39*, 1062–1068.

Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P. … & LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, *23*, 2129–2170.

Guy, W. (1976). *Abnormal Involuntary Movement Scale (AIMS)*. In ECDEU assessment manual for psychopharmacology (pp. 534–537). Rockville, MD: National Institute of Mental Health.

Honer, W.G., Kopala, L.C., & Rabinowitz, J. (2005). Extrapyramidal symptoms and signs in first-episode, antipsychotic exposed and non-exposed patients with schizophrenia or related psychotic illness. *Journal of Psychopharmacology*, *19*, 277–285.

ICD-10 (1992). *The ICD-10 classification of mental and behavioral disorders. Clinical and diagnostic guidelines*. Geneva, Switzerland: World Health Organization.

Janno, S., Holi, M.M., Tuisku, K., & Wahlbeck, K. (2005). Validity of Simpson-Angus Scale (SAS) in a naturalistic schizophrenia population. *BMC Neurology*, *5*, 5.

Kamis, D., Stratton, L., Calvo, M., Padilla, E., Florenzano, N., Guerrero, G. . . . & de Erausquin, G.A. (2015). Sex and laterality differences in parkinsonian impairment and transcranial ultrasound in never-treated schizophrenics and their first degree relatives in an Andean population. *Schizophrenia Research*, *164*, 250–255.

Kapur, S., & Mamo, D. (2003). Half a century of antipsychotics and still a central role for dopamine D2 receptors. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *27*, 1081–1090.

Kapur, S., & Seeman, P. (2001). Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. *American Journal of Psychiatry*, *158*, 360–369.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*, 980–988.

Keefe, R.S., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia Research*, *68*, 283–297.

Knol, W., Keijsers, C.J., Jansen, P.A., Belitser, S.V., Schobben, A.F., Egberts, A.C., . . . & van Marum, R.J. (2009). Validity and reliability of the Simpson-Angus Scale (SAS) in drug induced parkinsonism in the elderly. *International Journal of Geriatric Psychiatry*, *24*, 183–189.

Koning, J.P., Tenback, D.E., Kahn, R.S., Van Schelven, L.J., & Van Harten, P.N. (2010). Instrument measurement of lingual force variability reflects tardive tongue dyskinesia. *Journal of Medical Engineering & Technology*, *34*, 71–77.

Kuznetsova, A., Brockhoff, P.B., & Christensen, R.H.B. (2013). *lmerTest: tests for random and fixed effects for linear mixed effect models (lmer objects of lme4 package)*. Retrieved from http://CRAN.R-project.org/package=lmerTest

Lingjaerde, O., Ahlfors, U.G., Bech, P., Dencker, S.J., & Elgen, K. (1987). The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatrica Scandinavica. Supplementum*, *334*, 1–100.

McCreadie, R.G., Srinivasan, T.N., Padmavati, R., & Thara, R. (2005). Extrapyramidal symptoms in unmedicated schizophrenia. *Journal of Psychiatric Research*, *39*, 261–266.

McLean, R.A., Sanders, W.L., & Stroup, W.W. (1991). A unified approach to mixed linear models. *American Statistician*, *45*, 54–64.

Messinger, J.W., Trémeau, F., Antonius, D., Mendelsohn, E., Prudent, V., Stanford, A.D., & Malaspina, D. (2011). Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. *Clinical Psychology Review*, *31*, 161–168.

Molina, J.L., Gonzalez, A.G., Florenzano, N., Padilla, E., Calvo, M., Guerrero, G., . . . Erausquin, G.A. (2016). Prediction of neurocognitive deficits by Parkinsonian Motor Impairment in Schizophrenia: A study in neuroleptic-naive subjects, unaffected first-degree relatives and healthy controls from an indigenous population. *Schizophrenia Bulletin*, *42*, 1486–1495.

Nelson, B., Whitford, T.J., Lavoie, S., & Sass, L.A. (2014). What are the neurocognitive correlates of basic self-disturbance in schizophrenia?: Integrating phenomenology and neurocognition. Part 1 (Source monitoring deficits). *Schizophrenia Research*, *152*, 12–19.

Olfson, M. (2009). Antipsychotic prescriptions for children and adolescents in the UK increased from 1993 to 2005. *Evidence-Based Mental Health*, *12*, 30.

Olfson, M., Blanco, C., Liu, L., Moreno, C., & Laje, G. (2006). National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Archives of General Psychiatry*, *63*, 679.

Olfson, M., Blanco, C., Liu, S.M., Wang, S., & Correll, C.U. (2012). National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Archives of General Psychiatry*, *69*, 1247.

Olfson, M., Crystal, S., Huang, C., & Gerhard, T. (2010). Trends in antipsychotic drug use by very young, privately insured children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*, 13–23.

Pagsberg, A.K., Jeppesen, P., Klauber, D.G., Jensen, K.G., Ruda, D., Stentebjerg-Olesen, M., . . .& Fagerlund, B. (2014). Quetiapine versus aripiprazole in children and adolescents with psychosis–protocol for the randomised, blinded clinical Tolerability and Efficacy of Antipsychotics (TEA) trial. *BMC Psychiatry*, *14*, 199.

Pagsberg, A.K., Jeppesen, P., Klauber, D.G., Jensen, K.G., Ruda, D., Stentebjerg-Olesen, M. . . . & Fink-Jensen, A. (2017). Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: The multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. *The Lancet Psychiatry*, *4*, 605–618.

Pearce, J.M. (2008). Observations on the blink reflex. *European Neurology*, *59*, 221–223.

Perry, W., Minassian, A., Paulus, M.P., Young, J.W., Kincaid, M.J., Ferguson, E.J., . . . & Geyer, M.A. (2009). A reverse-translational study of dysfunctional exploration in psychiatric disorders: from mice to men. *Archives of General Psychiatry*, *66*, 1072.

Pham, A. (2009). *E3: Microsoft shows off gesture control technology for Xbox 360*. The effort aims to attract a broader audience to Microsoft's console. Most of the 30 million Xbox 360s sold since November 2005 have been snapped up by avid young males drawn to complex shooter or adventure games such as Halo and Modern Warfare or R.P.Gs. Los Angeles Times.

Prosser, E.S., Csernansky, J.G., Kaplan, J., Thiemann, S., Becker, T.J., & Hollister, L.E. (1987). Depression, parkinsonian symptoms, and negative symptoms in schizophrenics treated with neuroleptics. *The Journal of Nervous and Mental Disease*, *175*, 100–105.

Putzhammer, A., & Klein, H.E. (2006). Quantitative analysis of motor disturbances in schizophrenic patients. *Dialogues in Clinical Neuroscience*, *8*, 123–130.

R Core Team (2014). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.

Rammer, J.R., Krzak, J.J., Riedel, S.A., & Harris, G.F. (2014). Evaluation of upper extremity movement characteristics during standardized pediatric functional assessment with a Kinect(R)-based markerless motion analysis system. *Conference of the IEEE Engineering in Medicine and Biology Society*, *2014*, 2525–2528.

Rocha, A.P., Choupina, H., Fernandes, J.M., Rosas, M.J., Vaz, R., & Silva Cunha, J.P. (2014). Parkinson's disease assessment based on gait analysis using an innovative RGB-D camera system. *Conference of the IEEE Engineering in Medicine and Biology Society*, *2014*, 3126–3129.

Rosenberg, M., Thornton, A.L., Lay, B.S., Ward, B., Nathan, D., Hunt, D., & Braham, R. (2016). Development of a Kinect Software Tool to Classify Movements during Active Video Gaming. *PLoS ONE*, *11*, e0159356.

Salonini, E., Gambazza, S., Meneghelli, I., Tridello, G., Sanguanini, M., Cazzarolli, C., . . . & Assael, B.M. (2015). Active video game playing in children and adolescents with cystic

fibrosis: Exercise or just fun? *Respiratory Care*, *60*, 1172–1179.
Sanchez, R., Calvo, J.M., & Jaramillo, L.E. (2005). Is the glabellar reflex a component of neuroleptic-induced Parkinsonism? *Biomedica*, *25*, 539–546.
Simpson, G.M., & Angus, J.W. (1970). A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica Supplementum*, *45*, 11–19.
Springer, S., & Yogev, S.G. (2016). Validity of the Kinect for gait assessment: A focused review. *Sensors*, *16*, 194.
Stentebjerg-Olesen, M., Jeppesen, P., Pagsberg, A.K., Fink-Jensen, A., Kapoor, S., Chekuri, R., … & Correll, C.U. (2013). Early nonresponse determined by the clinical global impressions scale predicts poorer outcomes in youth with schizophrenia spectrum disorders naturalistically treated with second-generation antipsychotics. *Journal of Child and Adolescent Psychopharmacology*, *23*, 665–675.
Stevens, J.R. (1978a). Disturbances of ocular movements and blinking in schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry*, *41*, 1024–1030.
Stevens, J.R. (1978b). Eye blink and schizophrenia: Psychosis or tardive dyskinesia? *American Journal of Psychiatry*, *135*, 223–226.
Takac, B., Catala, A., Rodriguez, M.D., van der Aa, N., Chen, W., & Rauterberg, M. (2013). Position and orientation tracking in a ubiquitous monitoring system for Parkinson disease patients with freezing of gait symptom. *JMIR mHealth and uHealth*, *1*, e14.
Tomita, Y., Shichida, K., Takeshita, K., & Takashima, S. (1989). Maturation of blink reflex in children. *Brain and Development*, *11*, 389–393.
Trémeau, F., Goldman, J., Antonius, D., & Javitt, D.C. (2013). Inpatients with schizophrenia report impaired situational motivation but intact global and social motivation. *Psychiatry Research*, *210*, 43–49.
Tupa, O., Prochazka, A., Vysata, O., Schatz, M., Mares, J., Valis, M., & Maril, V. (2015). Motion tracking and gait feature estimation for recognising Parkinson's disease using MS Kinect. *Biomedical Engineering Online*, *14*, 97.
Walther, S., Horn, H., Razavi, N., Koschorke, P., Muller, T.J., & Strik, W. (2009). Quantitative motor activity differentiates schizophrenia subtypes. *Neuropsychobiology*, *60*, 80–86.
Walther, S., Horn, H., Razavi, N., Koschorke, P., Wopfner, A., Muller, T.J., & Strik, W. (2010). Higher motor activity in schizophrenia patients treated with olanzapine versus risperidone. *Journal of Clinical Psychopharmacology*, *30*, 181–184.
Walther, S., Koschorke, P., Horn, H., & Strik, W. (2009). Objectively measured motor activity in schizophrenia challenges the validity of expert ratings. *Psychiatry Research*, *169*, 187–190.
Wing, J.K., Babor, T., Brugha, T., Burke, J., Cooper, J.E., Giel, R., … & Sartorius, N. (1990). SCAN. Schedules for clinical assessment in neuropsychiatry. *Archives of General Psychiatry*, *47*, 589–593.
Wolff, A.L., & O'Driscoll, G.A. (1999). Motor deficits and schizophrenia: The evidence from neuroleptic-naive patients and populations at risk. *Journal of Psychiatry and Neuroscience*, *24*, 304–314.
Zhao, J., Bunn, F.E., Perron, J.M., Shen, E., & Allison, R.S. (2015). Gait assessment using the Kinect RGB-D sensor. *Conference of the IEEE Engineering in Medicine and Biology Society*, *2015*, 6679–6683.

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Exploring Movement Impairments in Patients with Parkinson's disease using the Microsoft Kinect Sensor

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Keywords: Parkinson's disease, hypokinesia, technology, movement disorders, computer-assisted diagnosis.

Abstract

BACKGROUND: Current assessments of motor symptoms in Parkinson's disease, as well as of antipsychotic-induced motor symptoms in psychiatric patients, are often limited to clinical rating scales.

OBJECTIVES: To develop a computer application using the Microsoft Kinect sensor to assess performance-related bradykinesia.

METHODS: The developed application (*Motorgame*) was tested in patients with Parkinson's disease and healthy controls. Participants were assessed with the Movement Disorder Society Unified Parkinson's disease Rating Scale (MDS-UPDRS) and standardized clinical side effect rating scales, i.e., UKU Side Effect Rating Scale and Simpson-Angus Scale. Additionally, tests of information processing (Symbol Coding Task) and motor speed (Token Motor Task), together with a questionnaire, were applied.

RESULTS: Thirty patients with Parkinson's disease and 33 healthy controls were assessed. In the patient group, there was a statistically significant ($p<0.05$) association between prolonged time of motor performance in the *Motorgame* and upper body rigidity and bradykinesia (MDS-UPDRS) with the strongest effects in the right hand ($p<0.001$). In the entire group, prolonged time of motor performance was significantly associated with higher Simson-Angus scale score rigidity score and higher UKU hypokinesia scores ($p<0.05$). A shortened time of motor performance was significantly associated with higher scores on information processing ($p<0.05$). Time of motor performance was not significantly associated with Token Motor Task, duration of illness, or hours of daily physical activity. The *Motorgame* was well accepted.

CONCLUSIONS: The *Motorgame* was able to detect common motor symptoms in Parkinson's disease in a statistically significant and clinically meaningful way, making it applicable for further testing in larger samples.

Introduction

Parkinson's disease (PD) is a progressive, degenerative movement disorder[1]. The neuropathology of PD is characterized by loss of dopamine neurons in the substantia nigra resulting in dysfunction of the nigrostriatal pathway, which lead to perturbations of control and regulation of intentional motor movement. Bradykinesia, rigidity and resting tremor are the cardinal motor symptoms of PD[2]. Parkinsonian bradykinesia is the very core symptom and correlates with loss of dopaminergic deficiency[3]; it involves difficulties in planning, initiating and executing movements and difficulties in performing various tasks[4]. As the disease progresses, postural instability often develops as a fourth cardinal symptom[5]. The standard quantitative assessment for evaluating PD bradykinesia as well as other PD symptoms is the Unified Parkinson's Disease Rating Scale (UPDRS)[6].
When blocking the nigrostriatal pathway by D2-receptor antagonists, i.e., with antipsychotics, symptoms similar to the ones observed in idiopathic PD can occur. Antipsychotic-induced parkinsonism is characterized by bradykinesia, rigidity and (variable) tremor, which reverse upon antipsychotic discontinuation[7;8]. In clinical practice, antipsychotic-induced motor side effects are usually assessed by clinical evaluation. However, a number of rating scales for the evaluation of motor side effects exist, including the Abnormal Involuntary Movement Scale (AIMS)[9], Simpson-Angus Scale (SAS)[10] and the Barnes Akathisia Rating Scale (BARS)[11]. Another commonly used rating scale is the UKU Side Effect Rating Scale (UKU is an acronym for the Danish name "Udvalg for Kliniske Undersøgelser", Task Force for Clinical Investigations)[12]. Although all the mentioned rating scales have undergone thorough scientific validation, the fact that the rating scales are observer-based inherently requires adequate training of clinicians in their use and makes these scales vulnerable to inter-observer variability[13-15]. Hence, objective methods to detect and quantify movement disorders are needed. Besides overcoming the issue of inter-observer variability, objective technology-based tools may well be usable for home monitoring of symptoms.
Computerized analysis of human movements has been investigated for more than three decades[16]. Until recently, human motion capture (the process of registering motion) has required an extensive setup, typically involving several cameras, structured light projectors, and special markers attached to the different relevant body parts that are tracked. With the introduction of the Microsoft Kinect system in 2010, a low-cost motion tracking technology has become available.
We have developed a simple game-like application using the Microsoft Kinect, in which the user is asked to push buttons on a computer screen in a specific sequence, while the application tracks the movement of the major joints in the upper body. The objectives for this work was to test the feasibility of the *Motorgame* in both clinical and non-clinical environments, and to study the degree to which the *Motorgame* can complement the traditional observer-based rating scales of PD related bradykinesia.

We hypothesized that the Kinect would be acceptable to patients and that higher scores on rigidity related tests would generally be associated with prolonged time of motor performance (TOMP).

More specifically, we hypothesized that:
1) Prolonged TOMP in the *Motorgame* will be associated with higher
    i) MD-UPDRS scores
    ii) SAS rigidity scores
    iii) UKU bradykinesia scores
2) Shortened TOMP in the *Motorgame* will be associated with higher
    i) Token Motor Test motor speed scores

ii) Symbol Coding Task information processing speed scores

Materials and Methods

Participants and in- and exclusion criteria

This study included patients (age ≥ 18 years) with idiopathic PD (ICD-10 G20.9)[2;17] and a maximum score of 2.5 on the Hoehn & Yahr scale (i.e., posturally stable)[18]. Exclusion criteria were dementia, current psychosis, or on current antipsychotic treatment. The patient group was sought to be matched 1:1 to healthy controls on age and sex. Exclusion criteria in the healthy control were: Parkinson's disease, dementia, current psychosis, or lifetime antipsychotic treatment.

Recruitment

Patients were recruited in the Capital Region of Denmark at the Department of Neurology, Bispebjerg University Hospital (n=3), and from neurologists in primary sector (n=27). Healthy controls (n=33) were recruited through local contacts, tennis clubs, and senior centres in the Capitol Region. The technical work was initiated in January 2013, and the first demonstration model was ready for data collection in June 2013. Data collection was initiated in February 2014 and proceeded until August 2016.

Data and Acquisition

The data for this study comes from the Microsoft Kinect v1 sensor[19], which we refer to as the Kinect or Kinect sensor. The Kinect contains a RGB (Red Green Blue device-dependent color model) camera, an infrared camera and an infrared projector. The infrared camera and projector make it possible to estimate the depth of each pixel acquired by the RGB camera. Thus, the video stream that comes from the Kinect at 30 frames per seconds includes the standard video from the RGB camera, and for each pixel we get a *D*-value, which is an estimate of the distance from the Kinect to the point seen by the camera. This type of data is referred to as RGB-D video. One of the main innovations of the Kinect is the skeletal tracking algorithm[20]. The skeletal tracking algorithm is based on the Random Forest prediction algorithm[21]. When using the Kinect sensor, the data provided by the algorithm consist of a multivariate time-series of measurements, where positional measurements for hands, wrists, elbows, shoulders, neck and head are provided as 3D world coordinates. We only used coordinates from the upper body in this study.
We implemented a game-like environment in order to record series of movements of the participants. We refer to this environment as the *Motorgame*.

Description of the Motorgame

The *Motorgame* was developed, so that the participant observed the upper body of a stickman figure on a computer screen that mirrored the movements of the participant (See Figure 1). First, the participant was asked to place themselves at a distance between 2 and 3 meters from the screen for optimal recording conditions. The participant was then asked to stretch out their arms. This was done for calibrating the arm length of the stickman figure. After this procedure, a message appeared on the screen stating that the participant should try to finish the upcoming tasks as fast and precisely as possible. Then the following tasks were split up into three levels (See Figure 2 and 3). Before each level a welcome screen appeared, indicating that the participant had to perform a different task at the next level. The participant needed to perform similar movements of the hands repeatedly, but the design of random appearance of the button made it hard to *learn* this task. A score was displayed on the top of the screen where the participant was awarded a higher score if they finished the task fast. In order to avoid interruptions during the recording, a training session was performed before the actual recording session.

Description of Data

When a participant played the entire *Motorgame*, the data were recorded in a comma separated text file. Each entry in the file corresponds to one frame from the RGB-D video, where the frames were recorded 30 times per second. The RGB-D video data were stored in a separate file. The *screen coordinates* were the 2D coordinates of the joints as seen on the screen when playing the game.

Assessments

All participants were assessed with standard neurological examination. Only patients with PD were assessed with the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[6]. All participants were assessed with the UKU Side Effect Rating Scale[12]; assessing symptoms similar to antipsychotic-induced side effects, including hypokinesia) and the Simpson-Angus Scale[10] (SAS; assessing symptoms similar to antipsychotic-induced parkinsonism). In addition, two subtests from the Brief Assessment of Cognition in Schizophrenia (BACS)[22] assessing attention and information processing speed (Symbol Coding Task) and motor speed (Token Motor Task) were conducted. All participants were assessed with the *Motorgame*. Finally, participants filled out a questionnaire developed by the authors for the present study, a 5-point Likert scale about comprehensibility of the instructions, personal evaluation, and preferred choice of test, which assessed their opinion about the *Motorgame* compared to the additional clinical assessments.
All assessments of the patients were administered by one medical doctor (DRU), who prior to this study received training in the UPDRS at the Department of Neurology, Bispebjerg University Hospital as well as training in the clinical rating scales for the evaluation of motor side effects by a post-doctoral-level psychiatrist (JN) at the Department of Psychiatry, Aalborg University Hospital. Assessment of the healthy controls were administered by DR and one medical student (SKR). DRU and SKR had attended a systematic BACS training program by two post-doctoral-level neuropsychologists (BF and JRMJ), in which the training procedure[23] was delineated in agreement with Dr. Richard Keefe from NeuroCog Trials.

Ethical considerations

The study was approved by The Committees on Health Research Ethics for the Capital Region of Denmark and the Danish Health Authority. The Danish Data Protection Agency journal number 2007-58-0015 approved the data collection and data storing.

Data from the Motorgame

Data from the *Motorgame* were multivariate time-series of varying length, hence a single play of the *Motorgame* generated a lot of data. For the reason of testing the value of the measurement with respect to bradykinesia, the only variable we extracted for this analysis was the time it took to finish each of the tasks in level 1 of the *Motorgame*. For a given participant we obtained 22 variables. These measurements can be seen as 22 repeated measurements for a given participant, but due to the differences in the tasks, i.e., how far the participant had to move their hand, these measurements were inherently different. Hence, no corrections for multiple comparisons were made, but the difference between measurements was accounted for in the statistical model by assigning a fixed effect to each task.
As the data did not fit a Gaussian distribution, natural logarithm transformation was used. Due to the log transformation, parameters can approximately be seen as percentwise increase/decrease in time it took to finish the tasks. For example, a parameter estimate of 0.06 for male participants indicated that it took 6% longer time to finish the tasks compared to females. This approximation is

good for low values of parameters due to the Taylor-expansion of the natural logarithm having the coefficient value of 1 for the linear term.

Statistical Methods

To analyze the data we used a linear mixed effect model[24] using the package lmer[25] for the R-programming language[26] that provided *p*-values for the fixed effect in the model. The model also included a general mean term and the error was assumed to be independent and identically distributed from a normal distribution.

$$ln(y) = \mu + T_j + Cx_{ijC} + Sx_{ijS} + H_{ijH} + Ax_{ijA} + Wx_{ijW} + SYx_{ijSY} + \varepsilon_i + \varepsilon$$

The terms in the model were, *y* the response (time in seconds it took to finish a single task in level 1), and on the right hand-side we had in the following order: μ as a general mean, T_j mean for each of the 22 tasks in level 1, *C* parameter for the clinical score, where x_{ij} was the value for that measurements on participant *i* in task *j*. *S* was the sex, *H* was the height, *W* the weight and *SY* the result of the Symbol Coding Task. The last two terms were ε_i, the random effect for participants, and finally the general error term.

All tests were two-sided with alpha=0.05 and without correction for multiple comparisons, as this was a feasibility study with exploratory analyses of the correlation between the clinical and Motorgame scores for the assessment of PD related bradykinesia.

Results

Demographic and disease specific characteristics are shown in Table 1. Thirty patients with PD and 33 healthy controls were assessed. All patients and healthy controls completed the entire session of the *Motorgame*. As fewer healthy control males consented to participate in the study, the intended matching for sex was not achieved and the male proportion was significantly higher in the patient group than in the healthy control group (60.0% vs. 30.3%, p=0.018). All 30 patients (100%) were right-handed. All, but one, (97%) in the healthy control group were right-handed. Results of the clinical assessments showed significant differences between the two study groups (Table 2). A significantly higher proportion of the healthy controls managed to complete the Token Motor Task without modifications (pushing or tipping the tokens) than in the PD group (p=0.001). Likewise, the PD group had significantly lower mean scores on the Token Motor Task (indicating reduced motor speed in the fingers) versus healthy controls (25.5±18.1 vs. 39.9±13.4, p=0.003). Furthermore, patients had significantly higher mean SAS total scores (indicator of rigidity; p<0.001) and hypokinesia UKU scores (indicator of bradykinesia; p<0.001) compared to the group of healthy controls. No significant difference in mean scores (SD) in the Symbol Coding Task (information processing speed) was found between the PD group (37.53 (13.62) and the healthy control group (41.42 (10.15); p=0.201).

Mixed model analysis

The results from the mixed model analyses of the effect of motor MDS-UPDRS items scores (part III) on the time of motor performance in the *Motorgame* are seen in Table 3. Since MDS-UPDRS was only assessed in patients with PD, all controls were assigned the value zero for the measured variables in this analysis, which is consistent with prior studies using the MDS-UPDRS in healthy controls[27;28]. Compared to zero, all motor items in the MDS-UPDRS corresponding to bradykinesia and rigidity in the upper body, except for finger tapping on the left and hand movements on the left, had a significant (p<0.05) effect on prolonging the time of motor performance in the *Motorgame*.

The strongest effects were from *finger tapping on the right*, *hand movements on the right*, and *rotation of the right hand* (items of bradykinesia; $p<0.001$). A negative moderating effect of Symbol Coding Task scores was found for all motor MDS-UPDRS items ($p<0.001$), i.e., a higher (better) information processing score corresponded to a shortened time of motor performance. No moderating effects of age or body weight were found. Significant ($p<0.05$) moderating effects of male sex (negative, i.e. shorter performance time) and height (positive, i.e., longer performance time) were found in the MDS-UPDRS items of finger tapping on the right, hand movements on the right, and rotation of the right hand, but not regarding the remaining motor MDS-UPDRS items scores.

Mixed model analysis - Clinical assessments

As seen in Table 4, SAS items scores corresponding to bradykinesia and rigidity, as well as the hypokinesia UKU score, had a significant ($p<0.05$) positive effect on the time of motor performance in the *Motorgame*. Furthermore, a negative, moderating effect of Symbol Coding Task scores was found in all SAS items ($p<0.001$). No significant effects of Token Motor Task (motor speed), duration of PD and hours of weekly physical activity were found. No moderating effects of age, height or weight were found.

Acceptance of the Motorgame

The application was well accepted and preferred over the clinical rating scales and the BACS subtests by 76% in the healthy control group and 53% in the patient group.

Discussion

Initially developed as an entertainment device, e.g., used for dancing games, the Kinect sensor is now in widespread research use, including neuro-rehabilitation[29], assessment of post-stroke movement impairment[30], and classification of movements during active video gaming[31].
In our study of 30 patients with PD and 33 healthy controls, we found a highly significant association between prolonged time of motor performance in the *Motorgame* and higher scores of MDS-UPDRS items related to right hand movements (bradykinesia).

Bradykinesia has been shown to correlate strongly with a broad cluster of PD motor symptoms[32]. Furthermore, 18 F-DOPA PET brain scans in PD patients with predominantly hypokinesia and rigidity motor symptoms correlate significantly with dopaminergic depletion in the striatum[33]. In our study, we found a statistically significant association between prolonged motor performance and upper-body rigidity (MDS-UPDRS).
The same associations between time of motor performance and bradykinesia and rigidity were found in relation to the clinical rating scales: i.e., prolonged time of motor performance in the *Motorgame* was related to higher rigidity SAS scores and UKU hypokinesia. However, surprisingly, we did not find a significant association between time of motor performance in the *Motorgame* (assessing gross motor skills) and motor speed (Token Motor Task; assessing fine motor skills). A possible explanation might be that the *Motorgame* is a more complex motor test demanding a high level of eye-hand coordination and cognitive skills. This was confirmed by the finding of a significant moderating effect of the Symbol Coding Task on the time of performance of the *Motorgame* (i.e., shortened time of performance was associated with higher/better scores of information processing).
Furthermore, we did not find an association between time of motor performance in the *Motorgame* the duration of PD. An explanation could be that the included group of patients in this study were

all well-medicated, which was reflected by their median (IQR) Hoehn and Yahr score of 2 (2-2) and that the mean (±SD) duration of illness was 45.7 months ± 34.0 months.
We found that males had a significantly faster performance time in the majority of the estimates, which is consistent with findings in healthy individuals[34]. Whether this difference is further accentuated by PD cannot be analyzed in our study due to the small sample size.
In line with a study of adaptive training/rehabilitation in patients with PD[35], we found a high level of participant acceptance of the *Motorgame,* showing that the *Motorgame* was the preferred choice of test by the majority of the healthy control group (76%) as well as in the patient group (53%).
Overall, our results are consistent with previous studies of the Kinect sensor used as a supplementary assessment for patients with PD. Galna and colleges studied the accuracy of the Kinect in 9 PD patients and 10 healthy controls comparing it to the Vicon three-dimensional motion analysis system[36]. They demonstrated a high accuracy of the Kinect sensor when measuring time and gross spatial characteristic movements relevant to PD and highly appropriate for distinguishing non-PD subjects from PD patients treated with deep brain stimulation. Likewise, the Kinect sensor has shown high validity regarding gait parameters when validated against a multiple-camera 3D motion capture system[37].

Strengths and limitations

The study has several strengths. Firstly, the instrument is low-cost, easily accessible, portable and easy to administer, and does not require expert clinical knowledge to use. Secondly, applicability to the clinical setting was tested and proven on several levels. In terms of practicality, the Kinect-based instrument was easy to set up in hospitals, in private houses, in tennis clubs and senior centers. The test bears potential to be carried out even in intensive care wards and in small examination rooms. Thirdly, the study showed that all PD participants and healthy controls completed the *Motorgame*. Previous studies have shown that videogames for patients with PD should not be made too difficult, in terms of their pace or cognitive complexity[38]. Fourthly, by including healthy controls, matched for age, which is one of the most important variables for variation in motor performance[34].

The study has some limitations. Firstly, our *Motorgame* only covers upper extremities and neck. Secondly, the version of the Kinect device used in the present study does not have the accuracy to detect tremor, at least not based on the motion trajectories computed by the internal Kinect algorithms. Potentially, tremor related measurements could be extracted from the raw Kinect depth-image information. However, due to the small sample size in this study, experimental data exploration of this kind was not possible. For this reason, we also excluded the tremor related clinical measurements from the analysis. Newer devices with higher accuracy are currently being developed, which potentially might enable tremor detection. Thirdly, healthy controls were not adequately matched to PD patients based on sex, which besides age is a second variable relevant to motor performance[34]. However, in our analyses, we covaried for sex, diminishing the effect that age could have had in the findings. Further, we limited ourselves to perform the analyses on a simple meta-variable (the playing time). However, the system is able to gather large amounts of data from the movement patterns of the tested participants. The reason for restricting the analysis to the level 1 task data is the potential problem of overfitting the sparse set of available movement related features such as speed, acceleration and deceleration, and even the use of more automated feature extraction techniques. These aspects should be taken into considerations in future studies.
Fourthly, the sample size in this study is small, thereby enhancing the risk of both type I and type II errors. However, the number of included patients was based on the prestudy power analysis and several of the hypotheses of the study were confirmed.

Fifthly, the PD patients were evaluated in a highly specialized university clinic, while the healthy controls were evaluated in tennis clubs and senior centres. However, 27(90%) patients was recruited from primary sector and the cohort can be seen as representative for the general population of PD patients. A larger scale study is needed for confirming these findings.

In conclusion, we have presented an easy to use system, the *Motorgame,* with data showing significant associations with currently used clinical motor scores. The concept of using a gamified measurement device showed high acceptability among the participants and high feasibility in both hospital and non-hospital environments. The *Motorgame* offers an accessible objective complementary tool to the traditional observer-based rating scales of motor disturbance symptoms. However, further development is needed to improve the tracking of tremor and motor symptoms in the lower extremities. The present data suggest the potential utility of using portable and accessible systems like this on a much larger scaler and in different patient groups.

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Documentation of Author Roles

Ditte Rudå (DRU) has initiated the study. DRU, Gudmundur Einarsson (GEI), Anne Sofie Schott Andersen (ASA), Jannik Boll Nielsen (JBN), Cristoph Correll (CCO), Kristian Winge (KWI), Line Katrine Harder Clemmesen (LHC), Rasmus R. Paulsen (RRP), Anne Katrine Pagsberg (AKP), and Anders Fink-Jensen (AFJ) have made important contributions to the study conception, design and protocol. DRU has collected the clinical data. DRU, GEI and ASA have led the manuscript drafting. DRU, AKP, AFJ, KWI, RRP and GEI have been involved in drafting and all authors have critically revised the manuscript. JBN, GEI, LHC and RRP have developed the application for the Kinect sensor. GEI has done the mixed model analysis.

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Reference List

(1) Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J et al. Parkinson disease. *Nat Rev Dis Primers* 2017; 3:17013.

(2) Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015; 30(12):1591-1601.

(3) Benamer HT, Oertel WH, Patterson J, Hadley DM, Pogarell O, Hoffken H et al. Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: part 1. Baseline and 3-month observations. *Mov Disord* 2003; 18(9):977-984.

(4) Moustafa AA, Chakravarthy S, Phillips JR, Crouse JJ, Gupta A, Frank MJ et al. Interrelations between cognitive dysfunction and motor symptoms of Parkinson's disease: behavioral and neural studies. *Rev Neurosci* 2016; 27(5):535-548.

(5) Prescott IA, Liu LD, Dostrovsky JO, Hodaie M, Lozano AM, Hutchison WD. Lack of depotentiation at basal ganglia output neurons in PD patients with levodopa-induced dyskinesia. *Neurobiology of disease* 2014; 71c.

(6) Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement disorders : official journal of the Movement Disorder Society* 2008; 23(15).

(7) Hausner RS. Neuroleptic-induced parkinsonism and Parkinson's disease: differential diagnosis and treatment. *J Clin Psychiatry* 1983; 44(1):13-16.

(8) Lopez-Sendon J, Mena MA, de Yebenes JG. Drug-induced parkinsonism. *Expert Opin Drug Saf* 2013; 12(4):487-496.

(9) Guy WNIoMHPRBECDEP. Abnormal Involuntary Movement Scale (AIMS). In: Guy W, editor. Rockville, Md.: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.

(10) Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta psychiatrica Scandinavica Supplementum* 1970; 212.

(11) Barnes TR. A rating scale for drug-induced akathisia. *The British journal of psychiatry : the journal of mental science* 1989; 154.

(12) Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta psychiatrica Scandinavica Supplementum* 1987; 334.

(13) Wolff AL, O'Driscoll GA. Motor deficits and schizophrenia: the evidence from neuroleptic-naive patients and populations at risk. *Journal of psychiatry & neuroscience : JPN* 1999; 24(4).

(14) Lohr JB, Caligiuri MP. Quantitative instrumental measurement of tardive dyskinesia: a review. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 1992; 6(4).

(15) Dean CE, Russell JM, Kuskowski MA, Caligiuri MP, Nugent SM. Clinical rating scales and instruments: how do they compare in assessing abnormal, involuntary movements? *Journal of clinical psychopharmacology* 2004; 24(3).

(16) Moeslund TB, Granum E. A Survey of Computer Vision-Based Human Motion Capture. *Computer Vision and Image Understanding* 2001; 81(3).

(17) The ICD-10 classification of mental and behavioural disorders, diagnostic criteria for research. Geneva: World Health Organization; 1993.

(18) Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17(5).

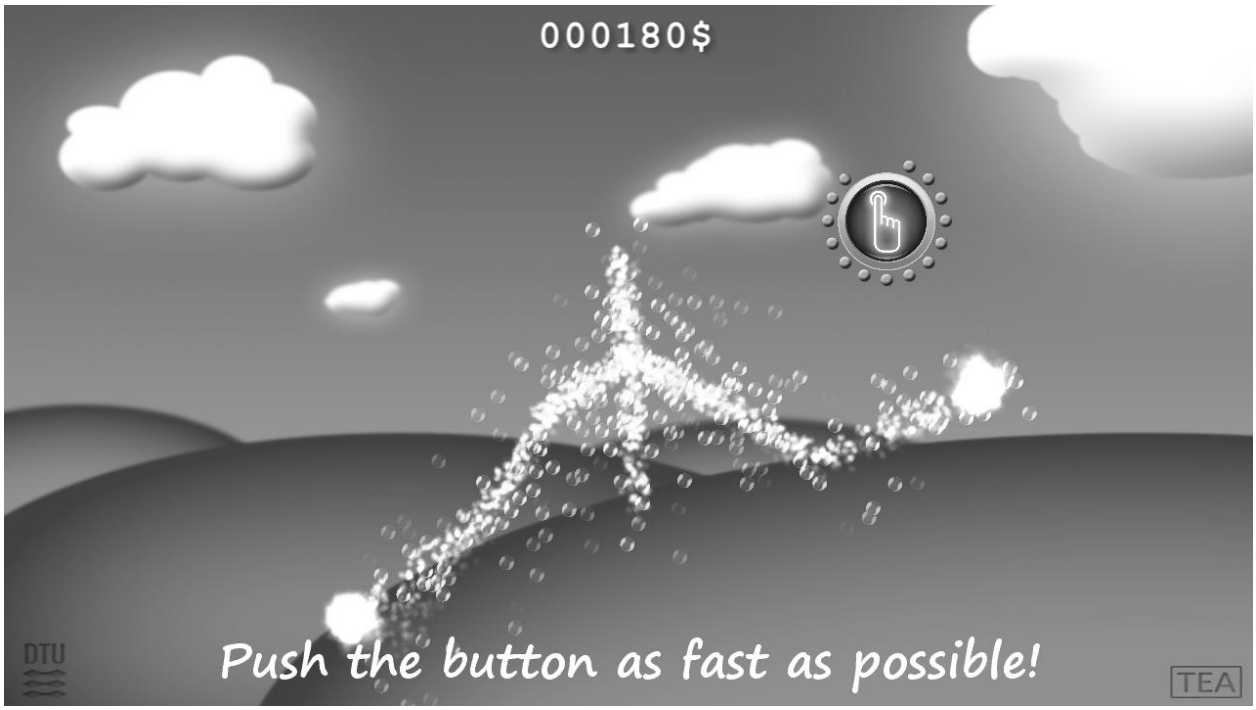
(19) Zhang Z. Microsoft Kinect Sensor and Its Effect. Journal IEEE MultiMedia archive Volume 19, Issue 2, 4-10. 2012. Los Alamitos, CA, USA, IEEE Computer Society Press.
Ref Type: Online Source
(20) Shotton J, Sharp T, Kipman A, Fitzgibbon A, Finocchio M, Blake A et al. Real-time human pose recognition in parts from single depth images. Communications of the ACM CACM Homepage archive Volume 56, Issue 1, 116-124. 2013. NY, USA, ACM New York.
Ref Type: Online Source
(21) Breiman L. Random Forest. Machine Learning (2001) 45: 5 . 2001. Kluwer Academic Publishers.
Ref Type: Online Source
(22) Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res* 2004; 68(2-3):283-297.
(23) Pagsberg AK, Jeppesen P, Klauber DG, Jensen KG, Ruda D, Stentebjerg-Olesen M et al. Quetiapine versus aripiprazole in children and adolescents with psychosis--protocol for the randomised, blinded clinical Tolerability and Efficacy of Antipsychotics (TEA) trial. *BMC Psychiatry* 2014; 14.
(24) McLean R.A. SWLSWW. A unified approach to mixed linear models. *Am Stat* 1991; 45:54-64.
(25) Kuznetsova ABPBCRHB. lmerTest: tests for random and fixed effects for linear mixed effect models (lmer objects of lme4 package). http://CRAN.R-project.org/package=lmerTest . 2013.
Ref Type: Online Source
(26) Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.2013. 2014.
Ref Type: Online Source
(27) Simuni T, Caspell-Garcia C, Coffey CS, Weintraub D, Mollenhauer B, Lasch S et al. Baseline prevalence and longitudinal evolution of non-motor symptoms in early Parkinson's disease: the PPMI cohort. *J Neurol Neurosurg Psychiatry* 2018; 89(1):78-88.
(28) Mollenhauer B, Zimmermann J, Sixel-Doring F, Focke NK, Wicke T, Ebentheuer J et al. Baseline predictors for progression 4 years after Parkinson's disease diagnosis in the De Novo Parkinson Cohort (DeNoPa). *Mov Disord* 2019; 34(1):67-77.
(29) Chang YJ, Chen SF, Huang JD. A Kinect-based system for physical rehabilitation: a pilot study for young adults with motor disabilities. *Research in developmental disabilities* 2011; 32(6).
(30) Olesh EV, Yakovenko S, Gritsenko V. Automated Assessment of Upper Extremity Movement Impairment due to Stroke. *PLoS One* 2014; 9(8).
(31) Rosenberg M, Thornton AL, Lay BS, Ward B, Nathan D, Hunt D et al. Development of a Kinect Software Tool to Classify Movements during Active Video Gaming. *PLoS One* 2016; 11(7):e0159356.
(32) Nieuwboer A, De WW, Dom R, Lesaffre E. A frequency and correlation analysis of motor deficits in Parkinson patients. *Disabil Rehabil* 1998; 20(4):142-150.
(33) Pikstra ARA, van der Hoorn A, Leenders KL, de Jong BM. Relation of 18-F-Dopa PET with hypokinesia-rigidity, tremor and freezing in Parkinson's disease. *Neuroimage Clin* 2016; 11:68-72.
(34) Jimenez-Jimenez FJ, Calleja M, Alonso-Navarro H, Rubio L, Navacerrada F, Pilo-de-la-Fuente B et al. Influence of age and gender in motor performance in healthy subjects. *J Neurol Sci* 2011; 302(1-2):72-80.
(35) Summa S, Basteris A, Betti E, Sanguineti V. Adaptive training with full-body movements to reduce bradykinesia in persons with Parkinson's disease: a pilot study. *J Neuroeng Rehabil* 2015; 12:16.
(36) Galna B, Barry G, Jackson D, Mhiripiri D, Olivier P, Rochester L. Accuracy of the Microsoft Kinect sensor for measuring movement in people with Parkinson's disease. *Gait Posture* 2014; 39(4):1062-1068.
(37) Arango Paredes JD, Munoz B, Agredo W, Ariza-Araujo Y, Orozco JL, Navarro A. A reliability assessment software using Kinect to complement the clinical evaluation of Parkinson's disease. *Conf Proc IEEE Eng Med Biol Soc* 2015; 2015:6860-6863.
(38) Mendes FAD PJLAdSKOTZAPM. Motor learning, retention and transfer after virtual-reality-based training in Parkinson's disease - effect of motor and cognitive demands of games: a longitudinal, controlled clinical study. Physiotherapy 2012, 98: 217-223.10.1016/j.physio.2012.06.001 . 2017.
Ref Type: Online Source

Figures and tables

Figure 1 A participant playing the Motorgame.

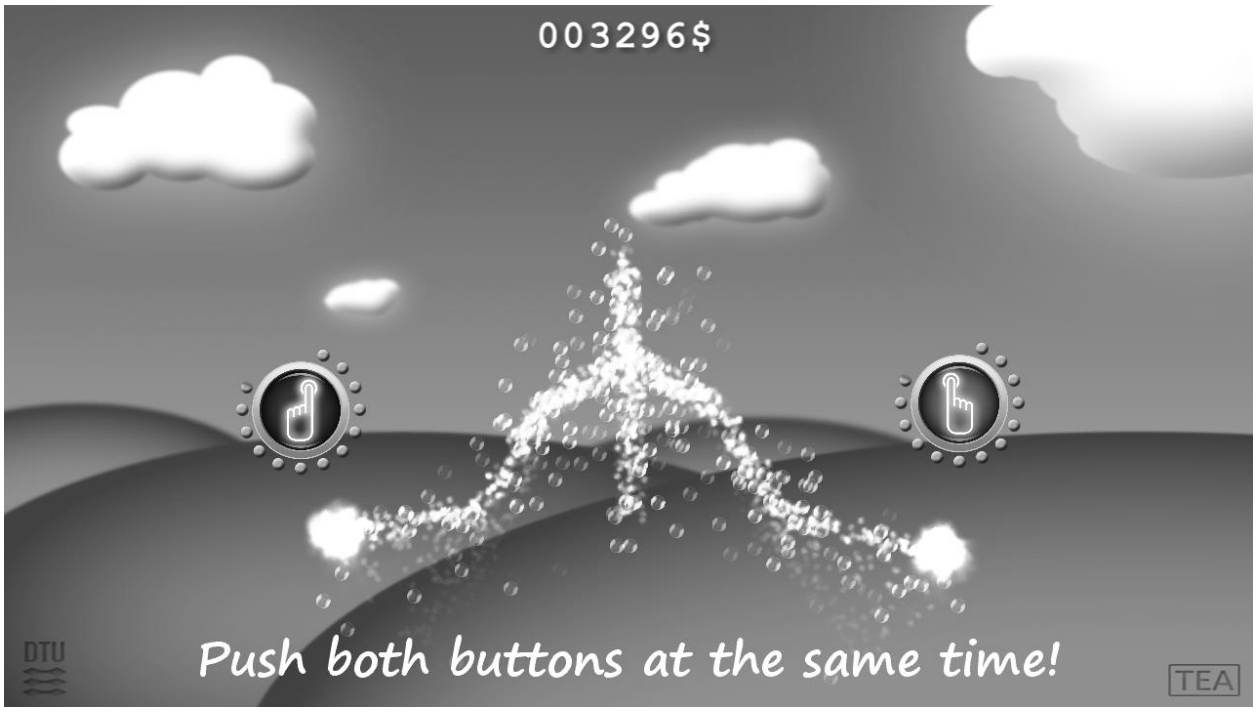
A Kinect sensor is placed on the top of the television/computer and tracks the participant's movements. The participant's pose is mirrored as a stickman figure on the screen.

Figure 2 Level 1 in the Motorgame from the participant's perspective.



The participant is moving its right hand upwards to reach the blue button visible on screen.

Figure 3 Level 2 in the Motorgame from the participant perspective.



Now the participant has to touch two buttons simultaneously.

513 **Table 1.** Demographic and disease specific characteristics

	Patients with Parkinson's Disease (n=30)	Healthy controls (n=33)	P value
Males, n (%)	18 (60.0)	10 (30.3)	**0.018**[a]
Age in years, mean (SD)	70.1 (6.7)	69.7 (6.1)	0.787[b]
Family history of Parkinson's Disease, n (%)	8 (26.7)	2 (6.1)	**0.025**[a]
Hoehn and Yahr score, median (IQR)	2 (2-2)	-	-
Mean duration of Parkinson's Disease in months, mean (SD)	45.7 (34.0)	-	-
L-dopa equivalent dose (Tomlinson CL 2010) mg, mean (SD)	868.4 (1902.2)	-	-
Physical activity hours/week, mean (SD)	6.6 (5.5)	7.7 (4.6)	0.388[b]
Computer games hours/week, mean (SD)	0.17 (0.91)	0 (0.0)	0.306[b]

514 *[a] chi² test; [b] unpaired t-test; "-" not applicable; SD Standard Deviation; IQR Interquartile Range*

515

516 **Table 2.** Clinical assessments

	Patients with Parkinson's Disease (n=30)	Healthy controls (n=33)	P value
BACS Token Motor Task (completers), n (%)	17 (56.67)	31 (93.94)	**0.001**[a]
BACS Token Motor Task score, mean (SD)	25.53 (18.13)	39.89 (13.44)	**0.003**[b]
BACS Symbol Coding Task, mean (SD)	37.53 (13.62)	41.42 (10.15)	0.201[b]
SAS total score, mean (SD)	0.87 (0.70)	0.13 (0.19)	**<0.001**[b]
Hypokinesia (item 2.3 UKU), mean (SD)	1.17 (0.65)	0.09 (0.29)	**<0.001**[b]

517 *[a] chi² test; [b] ANOVA test; SD Standard Deviation*

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Table 3 The effect of motor items in the MDS-UPDS on the time of motor performance in the Motorgame.

	MDS-UPDRS item	Sex	Age	Height	Weight	Symbol Coding Task
3.3a Rigidity Neck	**0.0401*** (0.0191)	-0.105 (0.0524)	-0.000552 (0.00307)	0.00517 (0.00349)	-0.00132 (0.00174)	**-0.00555**** (0.00161)
3.3b Rigidity Right Arm	**0.0447*** (0.0185)	-0.0994 (0.051)	0.000343 (0.00306)	0.00542 (0.00343)	-0.00136 (0.00171)	**-0.00509**** (0.00162)
3.3c Rigidity Left Arm	0.0372 (0.019)	-0.0916 (0.0516)	0.000325 (0.00313)	0.00525 (0.00351)	-0.00133 (0.00175)	**-0.0051**** (0.00167)
3.3d Rigidity Right Leg	**0.0351*** (0.0156)	-0.0946 (0.0511)	-0.000163 (0.00306)	0.00543 (0.00346)	-0.00174 (0.00171)	**-0.00508**** (0.00164)
3.3e Rigidity Left Leg	**0.0364*** (0.0165)	-0.0876 (0.0509)	-0.000624 (0.00306)	0.00515 (0.00348)	-0.00159 (0.00171)	**-0.00497**** (0.00166)
3.4a Finger Tapping Right Hand	**0.0528**** (0.0149)	**-0.135**** (0.0502)	0.000949 (0.00291)	**0.00799*** (0.00328)	-0.00203 (0.0016)	**-0.00517**** (0.0015)
3.4b Finger Tapping Left Hand	0.0308 (0.0161)	-0.103 (0.0527)	-0.000768 (0.00309)	0.00581 (0.00349)	-0.00114 (0.00177)	**-0.00562**** (0.00161)
3.5a Hand Movements Right	**0.0583**** (0.0162)	**-0.116*** (0.0486)	0.00106 (0.0029)	**0.00757*** (0.00325)	-0.00163 (0.0016)	**-0.00508**** (0.0015)
3.5b Hand Movements Left	0.024 (0.0167)	-0.0872 (0.0523)	-0.000534 (0.00314)	0.00546 (0.00357)	-0.00123 (0.00181)	**-0.00567**** (0.00165)
3.6a Pronation-Supination Movements of Hands Right	**0.06**** (0.0163)	**-0.12*** (0.0486)	0.00066 (0.00287)	**0.00804*** (0.00326)	-0.002 (0.00159)	**-0.0053**** (0.00149)
3.6b Pronation-Supination Movements of Hands Left	**0.0302*** (0.0148)	-0.0841 (0.0511)	-0.000763 (0.00308)	0.00535 (0.00349)	-0.00129 (0.00174)	**-0.00564**** (0.0016)
3.12 Postural Stability	0.0201 (0.0229)	-0.0839 (0.053)	-0.000243 (0.00321)	0.00642 (0.00359)	-0.00183 (0.00178)	**-0.00601**** (0.00164)
3.13 Posture	0.0438 (0.0218)	-0.0969 (0.0519)	-0.00101 (0.00308)	0.00592 (0.00348)	-0.00145 (0.00174)	**-0.00573**** (0.0016)
3.14 Global Spontaneity of Movement (Body Bradykinesia)	**0.0419*** (0.0183)	**-0.111*** (0.0525)	-0.000369 (0.00305)	0.00515 (0.00347)	-0.000732 (0.00178)	**-0.00517**** (0.00163)

*Results are logtransformed (natural logaritme). Each parameter estimate is presented with the standard deviation in parenthesis (SD). * $p<0.05$; ** $p<0.001$.*

Table 4 The effect of clinical assessment scores (Simpson Angus Scale, UKU and Token Motor task) and disease related characteristics on the time of motor performance in the Motorgame.

	Clinical assessment score	Sex	Age	Height	Weight	Symbol Coding Task l
SAS-1 Gait	**0.0613* (0.025)**	**-0.1028* (0.051)**	-0.00004 (0.003)	0.0050 (0.003)	-0.0008 (0.002)	**-0.0046* (0.002)**
SAS-2 Arm drop	**0.0717* (0.024)**	-0.0938 (0.049)	-0.0009 (0.003)	0.0040 (0.003)	-0.0009 (0.002)	**-0.0046* (0.002)**
SAS-3 Shoulder shaking	**0.0766* (0.023)**	**-0.1016* (0.049)**	-0.0001 (0.003)	0.0041 (0.0033)	-0.0008 (0.002)	**-0.0044*(0.002)**
SAS-4 Elbow rigidity	**0.0441*(0.017)**	**-0.1044* (0.051)**	0.0002 (0.003)	0.0053 (0.003)	-0.0012 (0.002)	**-0.0052* (0.002)**
SAS-5 Wrist rigidity	**0.0742* (0.026)**	**-0.1020* (0.050)**	-0.0004 (0.003)	0.0052 (0.003)	-0.0014 (0.002)	**-0.0053* (0.002)**
SAS-6 Leg pendulousness	**0.0369*(0.013)**	-0.0955 (0.050)	-0.0006 (0.003)	0.0051 (0.003)	-0.0013 (0.002)	**-0.0053* (0.002)**
SAS-7 Head dropping	**0.0431* (0.019)**	**-0.1071* (0.052)**	-0.0007 (0.003)	0.0051 (0.003)	-0.0012 (0.002)	**-0.0056** (0.002)**
SAS-8 Glabella tap	**0.0323* (0.011)**	-0.0813 (0.051)	0.0005 (0.003)	0.0046 (0.004)	-0.0010 (0.002)	**-0.0049* (0.002)**
SAS-9 Tremor	0.0162 (0.018)	-0.0824 (0.053)	-0.0010 (0.003)	0.0059 (0.004)	-0.0019 (0.002)	**-0.0061** (0.002)**
SAS-10 Salivation	0.0987 (0.056)	-0.0929 (0.052)	-0.0002 (0.003)	0.0061 (0.004)	-0.0014 (0.002)	**-0.0056* (0.002)**
2.3 Hypokinesia (UKU)	**0.0665* (0.022)**	**-0.1128* (0.050)**	-0.0008 (0.003)	0.0047 (0.003)	-0.0002 (0.002)	**-0.0052* (0.002)**
Token Motor Task	-0.0012 (0.001)	-0.0852 (0.054)	-0.0005 (0.003)	0.0061 (0.004)	-0.0017 (0.002)	**-0.0054*(0.002)**
Duration of Parkinson	0.0009 (0.000)	-0.1010 (0.053)	-0.0000 (0.003)	0.0072 (0.003)	-0.0018 (0.002)	**-0.0056*(0.002)**
Physical activity	0.0001 (0.003)	-0.0791 (0.054)	-0.0006 (0.003)	0.0062 (0.004)	-0.0019 (0.002)	**-0.0061** (0.002)**

Duration of Parkinson's Disease (PD) is in months. Physical activity is average number of hours per week.
** p<0.05; ** p<0.001.*

CYP2D6 genotyping and antipsychotic-induced extrapyramidal side effects in a randomized trial of aripiprazole versus quetiapine extended release in children and adolescents, aged 12-17 years, with first episode psychosis.

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Abstract

Objective: To study the association between genetically predicted CYP2D6 phenotypes and extrapyramidal symptoms (EPS).

Materials: Data from the Tolerability and Efficacy of Antipsychotics (TEA) trial of adolescents with first-episode psychosis randomized to aripiprazole versus quetiapine-ER were studied. EPS assessments included Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS). Patients were CYP2D6 genotyped. Plasma concentrations of antipsychotics and antidepressants were analysed.

Results: 113 youths (age=12-17 years; males=30%; antipsychotic-naïve=51%) were enrolled. High incidence of akathisia in both treatment arms (aripiprazole=47% and quetiapine-ER=32%; p=0.116) and a significantly higher mean global BARS score (±SD) in the aripiprazole versus quetiapine-ER arm ((1.45±1.19 versus 0.9±1.00, p=0.012) was found only at week 4, a difference that countervailed at week 12. At week 4, a significantly higher incidence of drug-induced parkinsonism was found in the aripiprazole than quetiapine-ER arm (37% versus 14%, p=0.011) as well as significantly higher SAS scores (±SD) (0.29±0.30 versus 0.17±0.25, p=0.023), a difference that attenuated over time. Poor metabolizers had a significantly higher dose-adjusted aripiprazole plasma concentration (±SD) compared to extensive metabolizers (week 4: 54.20±14.28 nmol/L/mg versus 33.11 ±13.71 nmol/L/mg; p=0.008; week 12: 49.40 ±24.61 nmol/L/mg versus 31.93 ±10.09 nmol/L/mg; p=0.054). This association was not found in the quetiapine-ER group. No association between CYP2D6 genotype groups and global BARS score or SAS score was found in any of the treatment arms.

Conclusion: Our results do not support routine use of CYP2D6 testing as a predictor of drug-induced parkinsonism or akathisia risk in clinical settings.

Trial registration: ClinicalTrials.gov: NCT01119014

Keywords: 2D6 genotyping, aripiprazole, quetiapine extended release, extrapyramidal symptoms, poor metabolizers.

Introduction

Aripiprazole and quetiapine are widely used for the treatment of both psychotic and non-psychotic disorders in children, adolescents and adults, with increasing prescription rates in Europe and in the US.[1-4] Both drugs are second-generation antipsychotics (SGAs), with an overall low liability for extrapyramidal symptoms (EPS) compared to first-generation antipsychotics.[5] EPS are associated with low quality of life and poorer daily functioning,[6;7] and poorer treatment compliance.[8;9] Risk factors for SGA-induced EPS include SGAs with potent dopamine receptor antagonism, history of previous EPS, and use of high doses.[10;11] Thus, factors contributing to higher drug plasma concentration levels, such as impaired drug metabolism, are likely to increase the risk of EPS. Aripiprazole and quetiapine are metabolized by hepatic cytochrome P450 (CYP) enzymes, CYP2D6 and CYP3A4. [12] Both enzymes are coded by genes that exert genetic polymorphism.[13] While the pharmacokinetics of aripiprazole are significantly associated with CYP2D6's phenotype[13], quetiapine is predominantly metabolized by CYP3A4. [14] CYP2D6 polymorphism has been known for decades and has been implemented in clinical settings to support dose individualization, whereas the clinical relevance of CYP3A4 polymorphism is less clear. Since EPS is dose dependent, it is reasonable to expect an increased risk of EPS in individuals with poor CYP2D6 metabolism and in medical treatment with aripiprazole.

Our aim was to study whether genetically predicted CYP2D6 phenotype is associated with EPS using data from the Tolerability and Efficacy of Antipsychotics (TEA) trial, a 12-week RCT comparing efficacy and safety of aripiprazole versus quetiapine extended release (-ER) in children and adolescents with first-episode psychosis.[15] Primary outcome (Positive and Negative Symptom

Scale score) and four key adverse outcomes (bodyweight, homoeostatic model of insulin resistance, akathisia and sedation)[16], cardio-metabolic status at baseline [17] and during the study[18;19], and verbal memory function[20] have already been published. Results about extrapyramidal side effects have been described in the main outcome paper from 2017[16]: Akathisia was significantly more likely with aripiprazole than with quetiapine-ER at week 2 (p=0.0021), but not at week 4 or week 12. At week 12, the least-squares-estimated sum scores on Simpson Angus Scale (SAS) were significantly higher with aripiprazole compared to quetiapine-ER (2.74 versus 1.31; p<0.0001). One aripiprazole-treated patient and no quetiapine-ER-treated patient developed dyskinesia (a score >2 on any AIMS subscale during intervention).

Materials

Study design: The TEA trial is a Danish investigator-initiated, multicenter, RCT in patients, age 12-17 years with first-episode psychosis, antipsychotic-naïve or treated for a limited period (no more than 12 months in the past year for psychosis, or no more than 1-week lifetime for any non-psychotic indication), 1:1 randomized to a 12- week, double-blind intervention with aripiprazole or quetiapine-ER. Rationale, design, methods and statistics have been described previously.[21] Briefly, patients followed a titration schedule with target doses of aripiprazole 20 mg/day versus quetiapine-ER 600 mg/day. For aripiprazole, the initial dose was 2.5 mg/day, increasing every second day to 5, 10, 15 and finally 20 mg/day on day 9. For quetiapine-ER, the initial dose was 50 mg/day, increasing every second day to 100, 200, 400 and finally 600 mg/day on day 9. If needed, dosing was flexible. Concomitant medication was allowed, except antipsychotic medication.

Assessments: Before inclusion, patients went through a comprehensive assessment program, including psychiatric symptom ratings, psychosocial and quality of life ratings, physical examination and ECG recording. Beneficial and harmful effects were assessed 2, 4, and 12 weeks

after randomization. Fasting blood samples were drawn at week 4 and 12. Steady state plasma trough concentrations of aripiprazole and quetiapine-ER were analyzed, as well as plasma concentration of frequently used antipsychotics (chlorprothixene, clozapine, haloperidol, olanzapine, paliperidone, risperidone) and antidepressants (amitriptyline, citalopram, fluoxetine, mianserin, mirtazapine, nortriptypline, sertraline, venlafaxine).

CYP2D6 *3, *4, *5, *6 gene deletion and CYP2D6 duplication were determined as described by Kobylecki et al.[22] Briefly, the determination of CYP2D6*3, *4 and *6 was done using commercially available 5' exonuclease-based reagents (Applied Biosystems Inc., Foster City, CA, USA); while deletion and duplication of CYP2D6 was determined by PCR and agarose gel electrophoresis of the amplified products. Patients were classified, according to their predicted phenotype as poor metabolizers (PMs), intermediate metabolizers (IMs), extensive (normal) metabolizers (EMs), or ultra-rapid metabolizers (UMs). We did not genotype for CYP3A4, since polymorphisms in the genes coding for CYP3A4 previously have shown extensive variation in expression and function and hence reduced clinical value.[23] EPS were assessed using the UKU Side Effect Rating Scale[24] (a 48-item scale assessing antipsychotic-induced side effects in 3 domains: psychic, neurological and autonomic; range 0-3), the Simpson-Angus scale (SAS) (a 10-item scale assessing antipsychotic-induced parkinsonism; range 0-4), the Abnormal Involuntary Movement Scale (AIMS)[25] (a 10-item scale assessing severity of facial, oral, extremity and trunk dyskinesias; range 0-4), and the Barnes Akathisia Rating Scale (BARS)[26] (a 4-item scale assessing objective and subjective aspects of akathisia; item 1-3 with a range of 0-3; the global score with a range of 0-5).

Data analysis: We used an intention to treat (ITT) approach. Descriptive analysis and simple group comparisons (aripiprazole versus quetiapine-ER) were performed using Pearson Chi-Square test for categorical data. Mann-Whitney test was used when comparing median cumulative doses of concomitant antipsychotics (protocol violation). Akathisia was defined by a BARS global score ≥ 2.

Drug-induced parkinsonism was defined as mean SAS score $\geq$ 0.33 (as proposed by Simpson et al).[27] Independent t-test was used for comparisons between treatment arms regarding global BARS scores and SAS scores and for comparisons between dose adjusted plasma concentrations of aripiprazole when used with/without concomitant sertraline. ANOVA was used to test for group differences between CYP2D6 genotype groups and dose adjusted plasma concentrations of aripiprazole, global BARS scores and SAS scores, respectively. All statistical analyses were conducted in SPSS (version 22+23).[28;29] Two-sided tests with alpha<0.05 were used.

Results

Baseline: 113 patients were enrolled in the study, 101 of whom were CYP2D6 genotyped. Baseline characteristics and demographics as well as CYP2D6 genotype groups are shown in table 1.

Drug discontinuation and treatment persistence: Although not statistically significant, patients in the aripiprazole arm more frequently discontinued trial medication before week 12 compared to the quetiapine-ER arm and had numerically shorter treatment persistence (table 2). Three discontinuations in the aripiprazole and none in the quetiapine-ER arm were due to EPS (two cases of akathisia, one case of hyperkinesia). There were no differences in the use of concomitant antipsychotic or antidepressant medication between treatments arms (table 2).

Extrapyramidal side effects: Frequency and degree of akathisia measured with the global BARS scores as well as frequency and degree of drug-induced parkinsonism, measured with the SAS score are shown in supplementary table 1. Patients in both treatment arms showed a high incidence of akathisia at week 4, but without significant difference between treatment arms (47% versus 32% p=0.116). The global BARS score ($\pm$SD) was significantly higher in the aripiprazole arm than the quetiapine-ER arm at week 4 (1.45$\pm$1.19 versus 0.90$\pm$1.00, p=0.012). At week 12, the global BARS

score had decreased significantly in the aripiprazole arm from 1.45±1.19 to 0.94±1.07 at week 12 (p=0.025) (supplementary table 1 and figure 2).

There was a significantly higher incidence of drug-induced parkinsonism in the aripiprazole arm than in the quetiapine-ER arm (37% versus 14%, p=0.011) and a higher SAS score (±SD) (0.29±0.30 versus 0.17±0.25, p=0.023) at week 4, a difference that attenuated over time (supplementary table 1, figure 2).

Anticholinergic medication, a proxy for drug-induced parkinsonism, was administered more frequently, although not statistically significantly, to aripiprazole-treated patients compared to quetiapine-ER-treated patients (20% versus 8% at week 4 and 12% versus 6% at week 12 ; p=0.067 and p=0.337, respectively).

Trial medicine doses and steady state: Mean dose (±SD) of administered aripiprazole was 15.05 (6.80) mg/day at the day before laboratory testing at week 4 and 15.22 (7.50) mg/day at week 12. Mean dose (±SD) of administered quetiapine-ER was 480 (182) mg/day at week 4 and 529 (182) mg/day at week 12. Mean plasma concentrations of aripiprazole are shown for each CYP2D6 genotype group in table 3. Among patients using concomitant SSRI (n=28) during the intervention period, only sertraline was verified in blood samples (in 14 patients, 7 patients in each treatment group) at time of assessment. We found no difference in dose adjusted plasma concentration of aripiprazole concentration (±SD) in patients with concomitant use of CYP2D6 inhibitors (SSRI, sertraline) (week 4: 35.79 (15.25) nmol/l/mg; week 12: 33.48 (12.27) nmol/l/mg) compared to patients with no concomitant use of CYP2D6 inhibitors (week 4: 36.07 (21.74) nmol/l/mg; week 12: 33.07 (9.42) nmol/l/mg; p =0.971 and p= 0.940, respectively). Similarly, there was also no significant difference in the quetiapine-ER group.

Associations between genotype groups and dose adjusted plasma concentration, global BARS score and SAS score: The dose adjusted plasma concentration of aripiprazole in PMs of CYP2D6 was

significantly higher compared to EMs at week 4 (p=0.008) and a borderline significantly higher at week 12 (p=0.054). PMs of CYP2D6 had borderline significantly higher dose adjusted plasma aripiprazole concentrations than IMs (p=0.097) and UMs (p=0.06) at week 4 (table 3 and figure 1). We found no association between quetiapine plasma concentrations and CYP2D6 genotype groups (table 3). No associations were found between CYP2D6 genotype groups and global BARS score, SAS scores or the use of anticholinergic medication in any of the treatment arms (table 3).

Discussion

The present study is a post-hoc analysis of EPS data from the TEA trial[16] with an aim of investigating if patients' genetically predicted CYP2D6 phenotype is associated with the risk of developing EPS. We found a high incidence of akathisia in both treatment arms at week 4 (47% in the aripiprazole arm and 32% in the quetiapine arm). The literature usually reports much lower incidence rates of akathisia in youth treated with these drugs, i.e. 6-15% for aripiprazole and 0-6% for quetiapine.[30] This difference might be due to the intensive monitoring of EPS in the TEA trial and the fact that akathisia is difficult to distinguish from anxiety, agitation and general restlessness, unless the rating is done by well-trained staff. We found correspondingly high levels of global akathisia scores (global BARS) with a significantly higher global BARS score in the aripiprazole arm compared to the quetiapine-ER arm at week 4, which is in line with previous findings indicating that akathisia usually is more frequently associated with the use of aripiprazole[31]. Interestingly, our results indicate that akathisia seems to wear off over time (from week 4 to week 12), despite the fact that the administered mean dose of aripiprazole and quetiapine-ER remained unchanged throughout the study, and was even slightly increased in the quetiapine-ER group. This supports previous findings from a 12-week, randomized comparison of risperidone and aripiprazole in young adults with first-episode psychosis where akathisia scores were found to be significantly

worse in the aripiprazole group compared to the risperidone group at week 1,4 and 6 only. However, at week 12, the akathisia scores in the aripiprazole group had decreased to the same low levels as in the risperidone group, thus indicating that akathisia might be, at least partly, a transient side effect.[32]

We found a significantly higher incidence of drug-induced parkinsonism in the aripiprazole arm compared to the quetiapine–ER arm at week 4, as well as more severe parkinsonism judged from the SAS score (±SD) (0.29 (0.30) versus 0.17 (0.25), p=0.023) and a correspondingly borderline significantly higher use of concomitant anticholinergic drugs (11 out of 54 versus 4 out of 52; p=0.067), a proxy for drug-induced parkinsonism. This finding indicates a clinically significant difference in drug-induced parkinsonism between treatment arms and is consistent with the high end of the range of previously reported incidence rates.[30]

Aripiprazole is mainly metabolized by CYP2D6, and previous studies have consistently shown that plasma concentrations of aripiprazole were significantly associated with the genetically predicted CYP2D6 phenotype.[33-36] Thus, we were not surprised to find significantly higher aripiprazole concentration in PMs compared to EMs. Likewise expected, we found no association between quetiapine plasma concentration and CYP2D6 genotype groups (table 3), as CYP2D6 only to a limited extent is involved in the metabolism of quetiapine. In our population, 6.2% of the aripiprazole group were PMs of CYP2D6. This is in line with genetic polymorphism studies showing that PMs account for approximately 7.7% among Caucasians.[37;38]

Despite the fact that PM status of CYP2D6 was associated with increased drug plasma concentrations, we found no association between decreased CYP2D6 metabolism and global BARS score or SAS score or differences in the number of patients treated with anticholinergic medication. The association between EPS and CYP2D6 polymorphism has previously been studied, but results are conflicting. Some studies have shown that PMs are significantly more likely to develop

parkinsonism [39-42] and have a higher risk of initiating anticholinergic medication (proxy for EPS) compared to EMs, [43] while others failed to do so.[44;45] The lack of a significant association in our study might be explained by the considerable overlap between dose adjusted plasma aripiprazole concentrations between PM, IM, EM and UMs (Figure 1), emphasizing the significant interindividual differences in dose-effect relationships of antipsychotics. Furthermore, the small sample size of PMs limited our power to detect statistical and clinically significant differences.

In theory, an existing association between CYP2D6 genotype groups and EPS could have been masked by clinicians' clinical dose adjustment, provided that CYP2D6 genotype had a strong clinical validity, i.e. the ability to predict a certain clinical outcome, so physicians easily could have detected patients' needs for dose adjustment clinically. However, we found no differences in administered aripiprazole doses between CYP2D6 genotype groups (table 3), which is in accordance with previous findings. [46] Another confounder could have been the concomitant intake of CYP2D6 inhibitors converting EMs of CYP2D6 to PMs (phenoconversion).[36] However, the only medication with moderate CYP2D6 inhibitor properties used in this study was sertraline, and there were no differences in dose adjusted plasma concentration levels of aripiprazole in individuals with and without concomitant sertraline.[47]

The results of this study need to be interpreted within its limitations. First, the study was primarily designed to study treatment efficacy and tolerability and was not powered to detect clinically relevant differences in genetic subpopulations, hence increasing the risk of type II errors. Second, the analyses in this paper were done post hoc and non-blinded (in contrast to the previously published results[16]), nevertheless, EPS ratings etc. were conducted prior to the unblinding of the study. Third, concomitant medication was allowed during the intervention. This fact reflects typical clinical practice, but also increases the risk of confounding effects. Concomitant medication was mainly administered as required and not registered in detail. Finally, the assessment of interrater

reliability was only carried out for PANSS ratings (primary outcome) and not for the EPS assessments. However, only well-trained nurses and doctors experienced in child and adolescent psychiatry were responsible for the assessments.

Conclusion and clinical implications: We found no significant association between CYP2D6 genotype groups and incidence and severity of EPS. Our findings do not support routine CYP2D6 genotyping in order to detect individuals with increased susceptibility to antipsychotic-induced EPS in a population of children and adolescents with first-episode psychosis. Instead, our results call for close and careful monitoring of EPS with clinical rating scales, since EPS predict poorer outcome in youth as well as in adults. Further long-term studies with larger sample sizes are needed.

Reference List

(1) Olfson M, Blanco C, Liu SM, Wang S, Correll CU. National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Archives of general psychiatry* 2012; 69(12).

(2) Birnbaum ML, Saito E, Gerhard T, Winterstein A, Olfson M, Kane JM et al. Pharmacoepidemiology of antipsychotic use in youth with ADHD: trends and clinical implications. *Curr Psychiatry Rep* 2013; 15(8):382.

(3) Rodday AM, Parsons SK, Correll CU, Robb AS, Zima BT, Saunders TS et al. Child and adolescent psychiatrists' attitudes and practices prescribing second generation antipsychotics. *J Child Adolesc Psychopharmacol* 2014; 24(2):90-93.

(4) Olfson M, King M, Schoenbaum M. Treatment of Young People With Antipsychotic Medications in the United States. *JAMA Psychiatry* 2015; 72(9):867-874.

(5) Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019; 394(10202):939-951.

(6) Gerlach J. Improving outcome in schizophrenia: the potential importance of EPS and neuroleptic dysphoria. *Ann Clin Psychiatry* 2002; 14(1):47-57.

(7) Tandon R, Lenderking WR, Weiss C, Shalhoub H, Barbosa CD, Chen J et al. The impact on functioning of second-generation antipsychotic medication side effects for patients with schizophrenia: a worldwide, cross-sectional, web-based survey. *Ann Gen Psychiatry* 2020; 19:42.

(8) Dibonaventura M, Gabriel S, Dupclay L, Gupta S, Kim E. A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. *BMC Psychiatry* 2012; 12:20.

(9) Kane JM. Addressing side effects from antipsychotic treatment in schizophrenia. *J Clin Psychiatry* 2011; 72(2):e07.

(10) Weiden PJ. EPS profiles: the atypical antipsychotics are not all the same. *J Psychiatr Pract* 2007; 13(1):13-24.

(11) Divac N, Prostran M, Jakovcevski I, Cerovac N. Second-generation antipsychotics and extrapyramidal adverse effects. *Biomed Res Int* 2014; 2014:656370.

(12) Buur-Rasmussen B, Brosen K. Cytochrome P450 and therapeutic drug monitoring with respect to clozapine. *Eur Neuropsychopharmacol* 1999; 9(6):453-459.

(13) Yang Y, Botton MR, Scott ER, Scott SA. Sequencing the CYP2D6 gene: from variant allele discovery to clinical pharmacogenetic testing. *Pharmacogenomics* 2017; 18(7):673-685.

(14) Caccia S. Biotransformation of post-clozapine antipsychotics: pharmacological implications. *Clin Pharmacokinet* 2000; 38(5):393-414.

(15) Pagsberg AK, Jeppesen P, Klauber DG, Jensen KG, Ruda D, Stentebjerg-Olesen M et al. Quetiapine versus aripiprazole in children and adolescents with psychosis--protocol for the randomised, blinded clinical Tolerability and Efficacy of Antipsychotics (TEA) trial. *BMC Psychiatry* 2014; 14.

(16) Pagsberg AK, Jeppesen P, Klauber DG, Jensen KG, Ruda D, Stentebjerg-Olesen M et al. Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: the multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. *Lancet Psychiatry* 2017.

(17) Jensen KG, Correll CU, Ruda D, Klauber DG, Stentebjerg-Olesen M, Fagerlund B et al. Pretreatment Cardiometabolic Status in Youth With Early-Onset Psychosis: Baseline Results From the TEA Trial. *J Clin Psychiatry* 2017.

(18) Jensen KG, Gartner S, Correll CU, Ruda D, Klauber DG, Stentebjerg-Olesen M et al. Change and dispersion of QT interval during treatment with quetiapine extended release versus aripiprazole in

children and adolescents with first-episode psychosis: results from the TEA trial. *Psychopharmacology (Berl)* 2018; 235(3):681-693.

(19) Jensen KG, Correll CU, Ruda D, Klauber DG, Decara MS, Fagerlund B et al. Cardiometabolic Adverse Effects and Its Predictors in Children and Adolescents With First-Episode Psychosis During Treatment With Quetiapine-Extended Release Versus Aripiprazole: 12-Week Results From the Tolerance and Effect of Antipsychotics in Children and Adolescents With Psychosis (TEA) Trial. *J Am Acad Child Adolesc Psychiatry* 2019; 58(11):1062-1078.

(20) Fagerlund B, Pantelis C, Jepsen JRM, Raghava JM, Rostrup E, Thomas MB et al. Differential effects of age at illness onset on verbal memory functions in antipsychotic-naive schizophrenia patients aged 12-43 years. *Psychol Med* 2020;1-11.

(21) Pagsberg AK, Jeppesen P, Klauber DG, Jensen KG, Ruda D, Stentebjerg-Olesen M et al. Quetiapine versus aripiprazole in children and adolescents with psychosis--protocol for the randomised, blinded clinical Tolerability and Efficacy of Antipsychotics (TEA) trial. *BMC Psychiatry* 2014; 14:199.

(22) Kobylecki CJ, Jakobsen KD, Hansen T, Jakobsen IV, Rasmussen HB, Werge T. CYP2D6 genotype predicts antipsychotic side effects in schizophrenia inpatients: a retrospective matched case-control study. *Neuropsychobiology* 2009; 59(4):222-226.

(23) Klein K, Zanger UM. Pharmacogenomics of Cytochrome P450 3A4: Recent Progress Toward the "Missing Heritability" Problem. *Front Genet* 2013; 4:12.

(24) Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987; 334:1-100.

(25) Guy W. Abnormal Involuntary Movement Scale (AIMS). Rockville, National Institute of Mental Health. 1976.

(26) Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989; 154:672-676.

(27) Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970; 212:11-19.

(28) IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. 2013.

Ref Type: Online Source

(29) IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. 2015.

Ref Type: Online Source

(30) Fraguas D, Correll CU, Merchan-Naranjo J, Rapado-Castro M, Parellada M, Moreno C et al. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. *Eur Neuropsychopharmacol* 2011; 21(8):621-645.

(31) Pagsberg AK, Tarp S, Glintborg D, Stenstrom AD, Fink-Jensen A, Correll CU et al. Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis. *J Am Acad Child Adolesc Psychiatry* 2017; 56(3):191-202.

(32) Robinson DG, Gallego JA, John M, Petrides G, Hassoun Y, Zhang JP et al. A Randomized Comparison of Aripiprazole and Risperidone for the Acute Treatment of First-Episode Schizophrenia and Related Disorders: 3-Month Outcomes. *Schizophr Bull* 2015; 41(6):1227-1236.

(33) Hendset M, Hermann M, Lunde H, Refsum H, Molden E. Impact of the CYP2D6 genotype on steady-state serum concentrations of aripiprazole and dehydroaripiprazole. *Eur J Clin Pharmacol* 2007; 63(12):1147-1151.

(34) Lisbeth P, Vincent H, Kristof M, Bernard S, Manuel M, Hugo N. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. *Eur J Clin Pharmacol* 2016; 72(2):175-184.

(35) van der Weide K, van der Weide J. The Influence of the CYP3A4*22 Polymorphism and CYP2D6 Polymorphisms on Serum Concentrations of Aripiprazole, Haloperidol, Pimozide, and Risperidone in Psychiatric Patients. *J Clin Psychopharmacol* 2015; 35(3):228-236.
(36) Kiss A, Menus A, Toth K, Deri M, Sirok D, Gabri E et al. Phenoconversion of CYP2D6 by inhibitors modifies aripiprazole exposure. *Eur Arch Psychiatry Clin Neurosci* 2020; 270(1):71-82.
(37) Shimizu T, Ochiai H, Asell F, Shimizu H, Saitoh R, Hama Y et al. Bioinformatics research on inter-racial difference in drug metabolism I. Analysis on frequencies of mutant alleles and poor metabolizers on CYP2D6 and CYP2C19. *Drug Metab Pharmacokinet* 2003; 18(1):48-70.
(38) Andersson T, Flockhart DA, Goldstein DB, Huang SM, Kroetz DL, Milos PM et al. Drug-metabolizing enzymes: evidence for clinical utility of pharmacogenomic tests. *Clin Pharmacol Ther* 2005; 78(6):559-581.
(39) Vandel P, Haffen E, Vandel S, Bonin B, Nezelof S, Sechter D et al. Drug extrapyramidal side effects. CYP2D6 genotypes and phenotypes. *Eur J Clin Pharmacol* 1999; 55(9):659-665.
(40) Crescenti A, Mas S, Gasso P, Parellada E, Bernardo M, Lafuente A. Cyp2d6*3, *4, *5 and *6 polymorphisms and antipsychotic-induced extrapyramidal side-effects in patients receiving antipsychotic therapy. *Clin Exp Pharmacol Physiol* 2008; 35(7):807-811.
(41) Armstrong M, Daly AK, Blennerhassett R, Ferrier N, Idle JR. Antipsychotic drug-induced movement disorders in schizophrenics in relation to CYP2D6 genotype. *Br J Psychiatry* 1997; 170:23-26.
(42) Fleeman N, Dundar Y, Dickson R, Jorgensen A, Pushpakom S, McLeod C et al. Cytochrome P450 testing for prescribing antipsychotics in adults with schizophrenia: systematic review and meta-analyses. *Pharmacogenomics J* 2011; 11(1):1-14.
(43) Schillevoort I, de BA, van der Weide J, Steijns LS, Roos RA, Jansen PA et al. Antipsychotic-induced extrapyramidal syndromes and cytochrome P450 2D6 genotype: a case-control study. *Pharmacogenetics* 2002; 12(3):235-240.
(44) Scordo MG, Spina E, Romeo P, Dahl ML, Bertilsson L, Johansson I et al. CYP2D6 genotype and antipsychotic-induced extrapyramidal side effects in schizophrenic patients. *Eur J Clin Pharmacol* 2000; 56(9-10):679-683.
(45) Plesnicar BK, Zalar B, Breskvar K, Dolzan V. The influence of the CYP2D6 polymorphism on psychopathological and extrapyramidal symptoms in the patients on long-term antipsychotic treatment. *J Psychopharmacol* 2006; 20(6):829-833.
(46) Jurgens G, Rasmussen HB, Werge T, Dalhoff K, Nordentoft M, Andersen SE. Does the medication pattern reflect the CYP2D6 genotype in patients with diagnoses within the schizophrenic spectrum? *J Clin Psychopharmacol* 2012; 32(1):100-105.
(47) Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 2002; 3(1):13-37.

Tables and Figures

Table 1. Baseline characteristics

	Aripiprazole (n=58)	Quetiapine-ER (n=55)	Total (n=113)
Age, years, mean (SD) (range 12-17)	15.7 (1.3)	15.8 (1.4)	15.7(1.4)
Males, n (%)	17 (29.3)	17 (30.9)	34 (30.1)
ICD-10 diagnoses, n (%)			
F20, Schizophrenia	42 (72.4)	33 (60.0)	75 (66.4)
F22, Delusional disorders	0 (0.0)	2 (3.6)	2 (1.8)
F23, Acute and transient psychotic disorders	1 (1.7)	0 (0.0)	1 (0.9)
F25, Schizoaffective disorders	9 (15.5)	14 (25.5)	23 (20.4)
F28, Other nonorganic psychotic disorders	2 (3.4)	2 (3.6)	4 (3.5)
F31, Bipolar disorders	1 (1.7)	0 (0.0)	1 (0.9)
F32, Depressive episode, psychotic	3 (5.2)	4 (7.3)	7 (6.2)
Psychopathology, mean (SD)			
PANSS total score (range 30-210)	78.6 (13.6)	77.2 (11.1)	77.9 (12.4)
GAPD scale score (range 0-8)	4.3 (1.1)	4.5 (1.1)	4.4 (1.1)
CYP2D6, n (%)			
Slow metabolizers	4 (6.9)	3 (5.5)	7 (6.2)
Intermediate metabolizers	17 (29.3)	17 (30.9)	34 (30.1)

2D6 genotyping and EPS

Extensive metabolizers	29 (50.0)	29 (52.7)	58 (51.3)
Ultrarapid metabolizers	1 (1.7)	1 (1.8)	2 (1.8)
Missing data	7 (12.1)	5 (9.1)	12 (10.6)
Smokers (cigarettes), n (%)	20 (34.5)	20 (36.4)	40 (35.4)
Antipsychotic treatment prior to inclusion, n (%)			
Antipsychotic-naïve	29 (50.0)	28 (50.9)	57 (50.5)
Limited, present* AP exposure	21 (38.2)	23 (39.7)	44 (38.9)
Limited, non-present AP exposure	6 (10.9)	6 (10.3)	12 (10.6)

Note: ER Extended Release; SD Standard Deviation; PANSS Positive and Negative Symptom Score (schizophrenia symptom severity); GAPD Global Assessment of Psychosocial Disability; CYP Cytochrome P450 enzymes; AP antipsychotic. *Present exposure: treatment within five days prior to inclusion; 10 days for aripiprazole due to longer half-life.

Table 2. Medication during intervention

	Aripiprazole (n=58)	Quetiapine-ER (n=55)	Total (n=113)	P value
Trial medicine, mean modal dose, mg (SD)	14.6 (6.8)	451.8 (198.9)	-	-
Days in trial medicine, mean (SD)	66.03 (27.3)	75.05 (23.8)	70.42 (25.9)	0.061[a]
Discontinuations, n (%)	20 (34.5)	11 (20.0)	31 (27.4)	0.085[b]
Any concomitant antipsychotic medication (acute), n (%)	22 (37.9)	19 (34.5)	41 (36.3)	0.708[b]
Concomitant antipsychotics, compounds				
Chlorprothixene, median cumulated dose, mg (IQR)	210 (105-1285)	310 (48.75-1616.25)	225 (105-1232.5)	0.887[a]
Olanzapine, median cumulated dose, mg (IQR)	440 (250-830)	85(21.25-425)	105 (25-515)	0.376[a]
Quetiapine, median cumulated dose, mg (IQR)	-	350 (350-359)	350 (350-350)	-
Any concomitant antidepresant medication, n (%)	15 (25.9)	13 (23.6)	28 (24.8)	0.784[b]
Concomitant antidepressants, compounds				
Setraline, mean dose, mg (SD)	85.0 (42.8)	67.9 (40.1)	77.9 (41.3)	0.418[c]
Fluoxetine, mean dose, mg (SD)	21.25 (8.3)	33.3 (11.5)	24.6 (10.4)	0.083[c]
Citalopram, mean dose, mg (SD)	10.0 (-)	25.0 (7.1)	77.9 (41.3)	0.333[c]
Paroxetine, mean dose, mg (SD)	20.0 (-)	-	20.0 (-)	-

Note: ER Extended Release; SD Standard Deviation; IQR Interquartile Range; CYP Cytochrome P450 enzymes; a Mann-Whitney Test; b Pearson Chi-Square test; c Independent t-test.

Table 3. Dose adjusted plasma concentrations of trial drug, BARS and SAS scores distributed by CYP 2D6 genotype groups

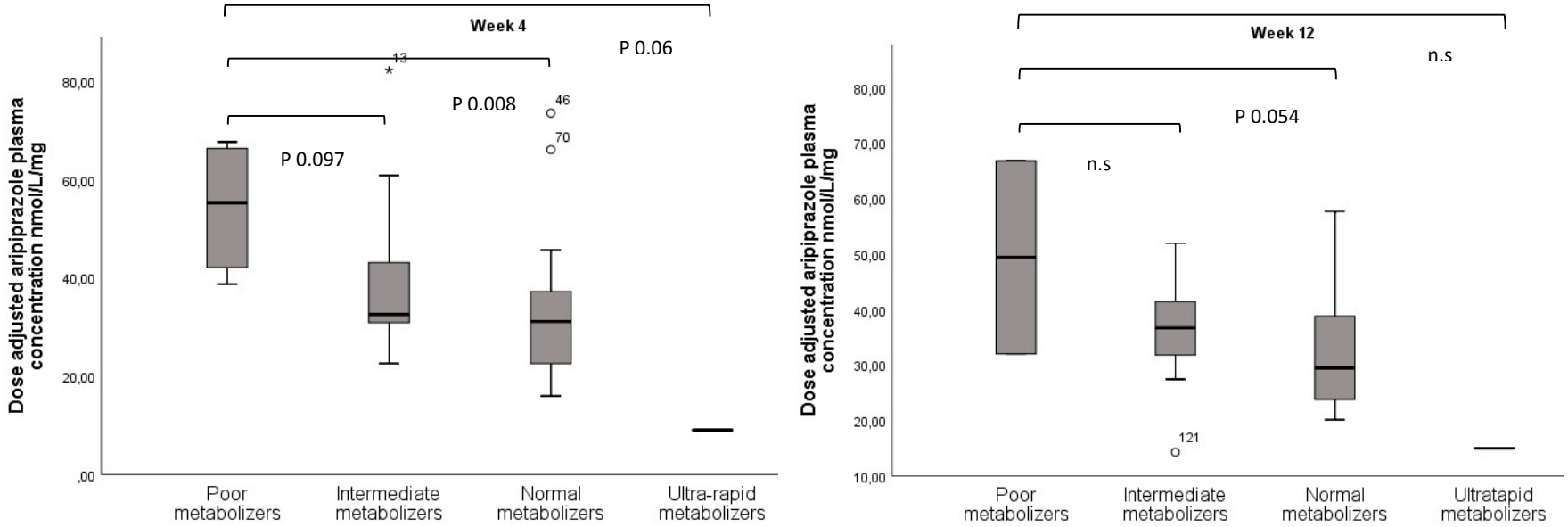
	Poor metabolizers (PM)	Intermediate metabolizers (IM)	Extensive metabolizers (EM)	Ultra-rapid metabolizers (UM)	P value
Aripiprazole group 51 patients with verified genotype					
Patients with valid blood sample, n (%)					
Week 4 (n=45)	4 (8.9)	14 (3.1)	26 (57.8)	1 (2.2)	-
Week 12 (n=32)	2 (6.2)	11 (34.4)	18 (56.3)	1 (3.1)	-
Trial medicine, mean dose*, mg (SD)					
Week 4	16.25 (4.79)	13.93 (6.56)	15.48 (7.42)	20.00 (-)	p=0.785[a]
Week 12	12.50 (3.54)	14.09 (9.17)	15.69 (6.52)	30.00 (-)	p=0.241[a]
Mean plasma concentration/trial medication dose, nmol/l/mg (SD)					
Week 4	54.20 (14.28)	38.50 (16.04)	33.11 (13.71)	9.05 (-)	**p=0.019[a]**
Week 12	49.40 (24.61)	36.15 (10.21)	31.93 (10.09)	15.00 (-)	**p=0.067[a]**
Use of concomitant anticholinergic medication, n (%)					
Week 4 (n=10)	0 (0.0)	3 (6.7)	7 (15.6)	0 (0.0)	-
Week 12 (n=4)	0 (0.0)	1 (3.1)	3 (9.4)	0 (0.0)	-
Patients with verified genotype and BARS assessment, n (%)					
Week 4 (n=47)	4 (8.5)	16 (34.1)	26 (55.3)	1 (2.1)	-

Week 12 (n=27)	0 (0.0)	11 (40.7)	16 (59.3)	0 (0.0)	-
Global BARS score, mean (SD)					
Week 4	1.25 (0.96)	1.06 (1.24)	1.65 (1.16)	3.00 (-)	p=0.240[a]
Week 12	-	1.00 (1.18)	0.56 (0.96)	-	p=0.301[a]
Patients with verified genotype and SAS assessment, n (%)					
Week 4 (n=46)	4 (8.7)	15 (32.6)	26 (56.5)	1 (2.2)	-
Week 12 (n=25)	0 (0.0)	9 (36.0)	15 (60.0)	1 (4.0)	-
SAS score, mean (SD)					
Week 4	0.18 (0.17)	0.35 (0.33)	0.30 (0.30)	0.30 (-)	p=0.774[a]
Week 12	-	0.20 (0.27)	0.22 (0.19)	0.50 (-)	p=0.450[a]
Quetiapine-ER group					
50 patients with verified genotype					
Patients with valid blood sample, n (%)					
Week 4 (n=43)	3 (7.0)	16 (37.2)	23 (53.5)	1 (2.3)	-
Week 12 (n=33)	3 (9.1)	11 (33.3)	19 (57.6)	0 (0.0)	-
Trial medicine, mean dose*, mg (SD)					
Week 4	533.33 (115.47)	550.00 (136.63)	404.35 (189.44)	800.00 (-)	**0.018[a]**
Week 12	600.00 (200.00)	563.64 (80.90)	497.37 (218.88)	-	0.502[a]
Mean plasma concentration/trial medication dose, nmol/l/mg (SD)					

Week 4	2.48 (1.65)	1.79 (1.04)	1.73 (1.21)	1.27 (-)	0.733[a]
Week 12	2.42 (1.43)	1.17 (0.50)	1.47 (1.15)	-	0.179[a]
Use of concomitant anticholinergic medication, n (%)					
Week 4 (n=4)	1 (2.3)	0 (0.0)	3 (7.0)	0 (0.0)	-
Week 12 (n=3)	1 (3.0)	0 (0.0)	2 (6.1)	0 (0.0)	-
Patients with verified genotype and BARS assessment, n (%)					
Week 4 (n=40)	3 (7.5)	15 (37.5)	22 (55.0)	0 (0.0)	-
Week 12 (n=34)	3 (8.8)	12 (35.3)	19 (55.9)	0 (0.0)	-
Global BARS score, mean (SD)					
Week 4	1.00 (1.00)	1.00 (1.20)	1.14 (0.94)	-	0.920[a]
Week 12	1.33 (1.53)	0.58 (1.00)	0.95 (1.47)	.	0.616[a]
Patients with verified genotype and SAS assessment, n (%)					
Week 4 (n=39)	3 (7.7)	15 (38.5)	21 (53.8)	0 (0.0)	-
Week 12 (n=32)	3 (9.4)	12 (37.5)	17 (53.1)	0 (0.0)	-
SAS score, mean (SD)					
Week 4	0.33 (0.42)	0.13 (0.14)	0.19 (0.30)	-	0.474[a]
Week 12	0.20 (0.26)	0.20 (0.23)	0.19 (0.19)	-	0.997[a]

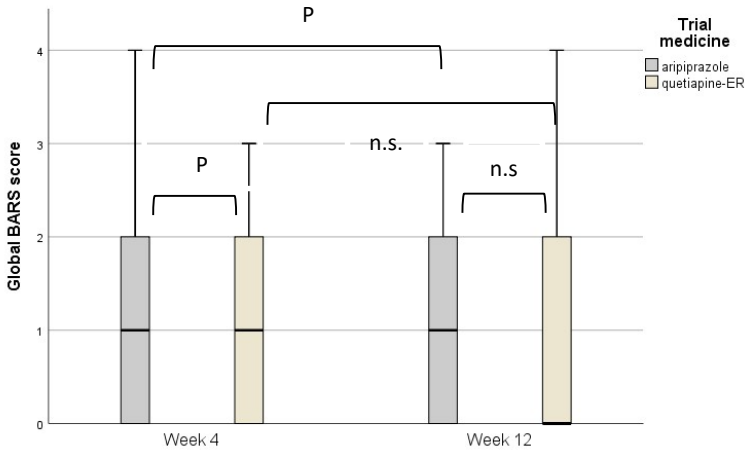
Note: SD Standard Deviation; BARS Barnes Akathisia Rating Scale; SAS Simpson Angus Scale; ER Extended Release; a ANOVA between group differences; * Trial medicine dose at the last day prior to laboratory testing; - Not applicable.

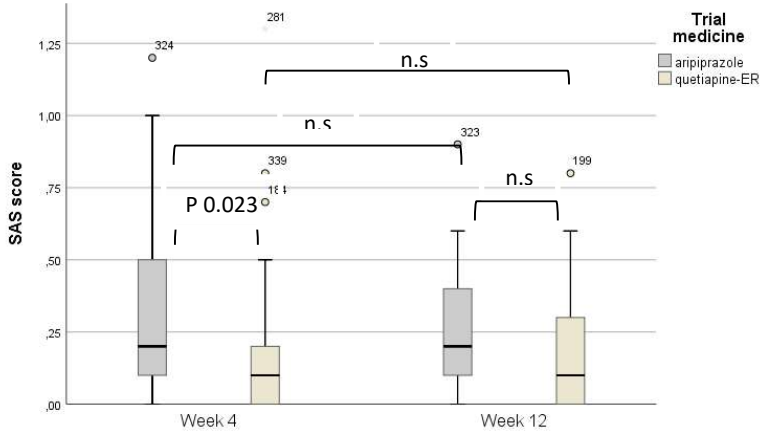
Figure 1. Boxplot of dose adjusted plasma concentration of aripiprazole distributed by genetically predicted Cytochrome 450 2D6 phenotypes



Note: n.s. non-significant

Figure 2 Mean global BARS scores (left) and mean SAS scores (right) distributed by trial medicine at week 4 and week 12





Note: BARS Barnes Akathisia Rating Scale; SAS Simpson Angus Scale; ER Extended Release; n.s. non-significant

Supplements

Supplementary table 1. Extrapyramidal side effects

	Aripiprazole	P value Within treatment arm	Quetiapine-ER	P value Within treatment arm	P value Between treatment arms
BARS assessments, n (missing)					
Week 4	53 (5)		50 (5)		
Week 12	47 (11)		48 (7)		
Global BARS score, mean (SD)					
Week 4	1.45 (1.19)	**0.025**[a]	0.90 (1.00)	0.870[a]	**0.012**[b]
Week 12	0.94 (1.07)	-	0.94 (1.26)	-	0.996[b]
Akathisia, n (%)					
Week 4	25 (47.2)	**0.045**[c]	16 (32.0)	0.936[c]	0.116[c]
Week 12	13 (27.7)	-	15 (31.25)	-	0.701[c]
SAS assessments, n (missing)					
Week 4	52 (6)		49 (6)		
Week 12	44 (14)		46 (9)		
SAS score, mean (SD)					
Week 4	0.29 (0.30)	0.314[a]	0.17 (0.25)	0.516[a]	**0.023**[b]
Week 12	0.24 (0.21)	-	0.20 (0.20)	-	0.349[b]
Drug-induced parkinsonism, n (%)					

Week 4	19 (36.5)	0.333[c]	7 (14.3)	0.231[c]	**0.011[c]**
Week 12	12 (27.3)	-	11 (23.9)	-	0.715[c]
Concomitant anticholinergic medication, n (%)					
Week 4	11 (20.4)	0.189[c]	4 (7.7)	0.696[c]	0.067[c]
Week 12	6 (12.2)	-	3 (6.0)	-	0.337[c]

Note: ER Extended Release; SD Standard Deviation; BARS Barnes Akathisia Rating Scale; SAS Simpson Angus Scale; a ANOVA; b Independent t-test; c Pearson Chi-Square test. Cases of akathisia were defined by a BARS global score $\geq$ 2 at any follow-up assessment. Cases of drug-induced parkinsonism were defined as an individual mean SAS score $\geq$ 0.33.