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Akathisia and atypical antipsychotics: relation to suicidality, agitation and depression in a clinical trial

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Original Article

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Abstract

Objective: Akathisia is among the most unpleasant side effects related to antipsychotic drug (AP) use, and possible associations between akathisia and agitation, depression and suicidal behaviour, respectively, have been described in previous literature. New generation antipsychotics are however regarded less prone to induce this particular adverse effect compared to older drugs, but evidence is incomplete and in need of confirmation from clinically relevant samples and settings. We, therefore, aim to investigate akathisia at hospital discharge for patients consecutively admitted with acute-phase psychosis and treated with atypical antipsychotics according to guideline-concordant clinical practice. *Methods:* This exploratory study is part of a naturalistic randomised controlled study in patients admitted with acute phase psychosis ($N = 109$). We report cross-sectional data at discharge/first follow-up after acute psychiatric hospital admission for patients with schizophrenia and related psychotic disorders. *Results:* There were statistically significant positive associations between akathisia and the following; suicidality in men (Beta 0.306, $p = 0.048$), but not in women; agitation in those previously unexposed to antipsychotics (Beta 0.288, $p = 0.047$) and depression in those exposed to antipsychotics before hospital admittance (Beta 0.375, $p = 0.031$). *Conclusion:* Main findings were that akathisia is still a prevalent side effect in a clinically relevant sample of patients treated with atypical antipsychotics. Our results suggest that akathisia is significantly associated with depression, suicidality and agitation in different subgroups of patients receiving APs. Akathisia can be detrimental and the relations between akathisia and depression, suicidality and agitation should be investigated further in prospective, hypothesis-testing studies with larger samples.

Significant outcomes/take home message

- The current findings support an association between akathisia and suicidality in men that is not previously reported.
- One should therefore consider screening for suicidality when men present with symptoms of antipsychotic-induced akathisia.
- We found a positive association between akathisia and agitation for those previously unexposed to antipsychotics.
- Clinicians should include akathisia as differential diagnosis when new motor or psychiatric symptoms of restlessness emerge during antipsychotic treatment.

Limitations

- Our results are based on analyses of cross-sectional data.
- Analyses of causality are therefore not possible.
- Akathisia is limited to subjective sensations reported by one single item of the UKU Side Effect Self-Rating Scale.
- The suicidality assessments is based solely on one item in the Calgary Depression Scale for Schizophrenia.

Trial registration

ClinicalTrials.gov ID; URL: http://www.clinicaltrials.gov/: NCT00932529.

Introduction

Antipsychotic drugs (APs) represent a cornerstone in the treatment of schizophrenia and related psychotic disorders, both in acute psychotic episodes and in the maintenance phase (Ceraso *et al.*, 2020; Kahn *et al.*, 2015). APs are however associated with troublesome side effects (Stroup & Gray, 2018) of which akathisia is regarded among the most debilitating (Kane *et al.*, 2009; Salem *et al.*, 2017). Akathisia is characterized by subjective feelings of inner restlessness and mental distress, objective motor restlessness caused by an urge for continuous movement (Factor *et al.*, 2019), and has been associated with intense dysphoria (Kane *et al.*, 2009), reduced quality of life and depression (Cem Atbasoglu *et al.*, 2001; Velligan *et al.*, 2017). Given the sometimes intense discomfort experienced by the patient, it seems plausible that akathisia may increase both suicidal behaviour and agitation, and indeed a putative association between akathisia and suicidality was suggested already four decades ago (Van Putten, 1975). However, due to the paucity of relevant data (Musco *et al.*, 2020), the association remains elusive (Aguilar & Siris, 2007; Kane *et al.*, 2009) though some associations towards increased suicide risk has been indicated (Cem Atbasoglu *et al.*, 2001; Hansen, 2001; Reutfors *et al.*, 2016), especially among patients with first-episode psychosis (Seemuller *et al.*, 2012; Seemüller *et al.*, 2012). Similar concerns have been raised about agitation related to akathisia (Cem Atbasoglu *et al.*, 2001), but the nature and magnitude of any associations still remains to be clarified at large.

Akathisia usually occurs within a few days to weeks after the administration of an AP or an increase in the dosage (Juncal-Ruiz *et al.*, 2017). Acute akathisia is less likely with atypical antipsychotics (AAPs) than with typical antipsychotics (Musco *et al.*, 2020) but the risk still remains substantial (Martino *et al.*, 2018) and acute akathisia is a highly relevant clinical phenomenon (Factor *et al.*, 2019; Yoshimura *et al.*, 2019). The incidence rates and prevalence of akathisia with AAP's range between 1% and 27% (Musco *et al.*, 2020). Predictors of acute akathisia except antipsychotic treatment remains unclear (Yoshimura *et al.*, 2019), but male gender seems to increase the risk, together with lower age as adolescents and previously untreated patients experiencing their first episode of psychosis (FEP) are particularly vulnerable to the development of akathisia (Musco *et al.*, 2020; Poyurovsky & Weizman, 2020).

Assembling the evidence for antipsychotic-associated movement disorders remains a challenge due to methodological heterogeneities across clinical trials, limitations in existing systematic reviews, in meta-analyses and literature overviews (Martino *et al.*, 2018). Thus, further research in akathisia is highly pertinent to clarify its potential roles related to suicidality, agitation and depression, to prevent unnecessary suffering and potentially fatal outcomes. Given the limited and equivocal literature on the potential associations between akathisia and these variables during treatment with AAP, a naturalistic exploratory study is needed to understand these phenomena as they occur in a real-life clinical settings and to guide clinical decisions and future research. Finally, most meta-analytical evidence is based on randomised, controlled trials with highly selected samples (Leucht *et al.*, 2008) estimated to represent only one-tenth of the population under investigation due to extensive exclusion criteria. Pragmatic and naturalistic studies have been called for to increase generalizability of the findings to routine clinical care (Leucht & Davis, 2020). The strength of pragmatic trials like ours is the wide variety of psychotic disorders included, exclusion criteria kept to a minimum and psychotropic drug use largely unrestricted by the trial design, thus mirroring real-world treatment conditions.

Aims of the study

The aims of this exploratory study were to investigate if akathisia is associated with suicidality, agitation and depression, while accounting for gender differences and previous AP use in patients treated for acute-phase psychosis.

Materials and Methods

Design

This study is a sub-study of the Bergen Psychosis Project (BPP), a naturalistic, rater-blind, randomised trial comparing four AAPs. Data on this sub-study comprises findings from the quality assurance part of the BPP, investigating all study drug groups collectively. The BPP was conducted at Haukeland University Hospital in Bergen, Norway, from March 2004 until February 2009. Johnsen *et al.* (2010) has further described BPP's rationale, methods and design in more detail.

Sample

The present paper reports data collected during the first phase of the BPP study. Eligible participants included all patients (aged ≥18) admitted to the emergency psychiatric ward with symptoms of psychosis as determined by a score of ≥4 on at least one of the items Delusions, Hallucinations, Grandiosity, Suspiciousness/Persecution or Unusual thought content on the Positive and Negative Syndrome Scale (PANSS) (Opler *et al.*, 1999). Included patients fulfilled diagnostic criteria according to the International Classification of Diseases (ICD-10) (World Health Organization, 2007) for schizophrenia (F20), schizophreniform disorder (F20.8), schizotypal disorder (F21), persistent delusional disorders (F22), acute and transient psychotic disorders (F23), schizoaffective disorder (F25), other non-organic psychotic disorders (F28), unspecified non-organic psychosis (F29), drug-induced psychosis (F1x.5) and major depressive disorder with psychotic features (F31.5, F32.3, F33.3). Further, eligible participants were candidates for oral AP therapy with a first-line AP. Drug-induced psychoses were included when the condition remained unresolved within a few days and when AP therapy was deemed indicated. Exclusion criteria included manic psychosis (F30.1), other behavioral or mental problems resulting in inability to cooperate with assessments, including organic brain disorders (dementia), agitation, hostility or pronounced suspiciousness towards the assessor, inability to use oral antipsychotics or already medicated with clozapine upon admittance, history of head injury or mental retardation, not understanding spoken Norwegian or being candidates for electroconvulsive therapy.

Procedure

Diagnoses were determined at discharge by the hospital's own psychiatrists or specialists in psychology. Data collection reported in the present study was undertaken at discharge/follow-up, maximally 11 weeks from baseline if still not discharged. Participants were determined antipsychotic naïve if they had never before used antipsychotic medications.

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Measures

The patient-administered version of the UKU Side Effect Self-Rating Scale (UKU SERS Pat) was used to assess the presence and severity of akathisia (Lindstrom *et al.*, 2001; Lingjaerde *et al.*, 1987). Akathisia is one (item 2.6) of 48 items of the scale with scoring option 0–3, where 0 indicates no symptom, and scores 1–3 indicate the presence of symptoms with increasing severity from mild to severe (0: *Not at all*, 1: *I like to keep moving around, but have no difficulty sitting or standing still (mild)*, 2: *I have to force myself to sit down or stand still (moderate)*, 3: *I have to keep walking around all the time (severe)*). The UKU SERS Pat was administered at discharge/follow-up only. The Calgary Depression Scale for Schizophrenia (CDSS) (Addington *et al.*, 1990) was used for assessing symptoms of depression and suicidality. The CDSS is the recommended scale for assessing depression symptoms in schizophrenia (Hasan *et al.*, 2015). The CDSS has demonstrated good predictive validity (Lako *et al.*, 2012), and distinguishes it better than other depression scoring tools depressive symptoms from negative and extra-pyramidal phenomena (Addington *et al.*, 1994). Both a modified version of the CDSS total score without the suicidality item (mCDSS) and the single suicidality item (CDSS item 8) were used in the analyses. Symptoms of psychosis were assessed by means of the PANSS which is a 30-item rating scale comprising seven items for positive symptoms, seven items for negative symptoms and 16 items for general psychopathology (Kay *et al.*, 1987), which is validity and reliability tested (Kay *et al.*, 1988). The BPP used the Structured Clinical Interview for the PANSS (SCI-PANSS), which was developed to secure reliable information for the PANSS scoring (Opler *et al.*, 1999). High interrater reliability was demonstrated among the raters for the PANSS with intra-class correlation coefficient 0.92. We further used the validated PANSS Excited Component (PANSS-EC) factor to assess agitation (Montoya *et al.*, 2011). The PANSS-EC consists of the five PANSS items: P4 Excitement, P7 Hostility, G4 Tension, G8 Uncooperativeness and G14 Poor impulse control (Lindenmayer *et al.*, 2004). Additional psychometric tools used were the Clinical Global Impression-Severity of Illness scale (CGI-S) (Guy, 1976), and the Global Assessment of Functioning, Split Version, Functions scale (GAF-F) (Karterud *et al.*, 1998).

Statistics

Categorical and continuous data were analysed in the SPSS software, version 24.0 (IBM SPSS Statistics, 2016). Cross-tabulation of categorical data was analysed by means of chi-square tests. ANOVA tests were used to analyse the differences between the group means in the sample. Post-hoc tests were utilized and adjusted with Bonferroni corrections for multiple testing. Analyses of associations between akathisia and depression, suicidality and agitation, respectively, were initially conducted by the means of Pearson and Spearman correlations. To adjust for potential confounding factors in the relationships between akathisia and depression, suicidality and agitation, linear regression analyses were undertaken with akathisia as the dependent variable, and modified CDSS sum score, the suicidality item of the CDSS, PANSS-EC and the Anxiety item (G2) of the PANSS as independent variables. Finally, depression, suicidality and agitation were entered as dependent variables, respectively, in separate linear regression models to explore the relationships among these and the other variables.

Table 1. Demographic and clinical characteristics at discharge ($N = 109$)

	n (%)
Diagnosis*	
Schizophrenia and related (F20, F21, F22, F25)	62 (56.9)
Drug-induced psychosis (F1x.5)	11 (10.1)
Affective psychosis (F31.5, F32.3, F33.3)	13 (11.9)
Acute psychosis (F23)	10 (9.2)
Other psychoses (F28, F29)	13 (11.9)
Antipsychotic naïve	51 (46.8)
Illicit substance use	32 (29.4)
	Mean (SD)
PANSS positive†	13.3 (4.7)
PANSS negative†	15.2 (6.6)
PANSS general†	26.3 (6.3)
PANSS total†	54.9 (14.4)
CDSS‡	3.9 (4.1)
CGI-S§	3.7 (1.1)
GAF-F#	38.8 (8.0)

*Diagnosis: Schizophrenia and related disorders: Schizophrenia, schizoaffective disorder, acute polymorphic psychotic disorder with symptoms of schizophrenia, acute schizophrenia-like psychotic disorder, delusional disorder; Acute psychosis = Acute psychosis other than those categorized under Schizophrenia and related; Affective psychosis = Bipolar and unipolar depression; Other psychoses = Miscellaneous psychotic disorders.
†Positive And Negative Syndrome Scale (PANSS).
‡Calgary Depression Scale for Schizophrenia (CDSS).
§Clinical Global Impression-Severity of Illness scale (CGI-S).
#The Global Assessment of Functioning Split Version Functions scale (GAF-F).

Ethics

The BPP was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. The first phase of the BPP was defined as a quality assurance project where only standard hospital routines were performed. For the quality assurance phase, the Regional Committee for Medical Research Ethics allowed eligible patients to be included before providing informed consent to the follow-up study. The present study reports data from the first phase of the BPP. The study was publicly funded and did not receive any financial or other support from the pharmaceutical industry. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975 (59th WMA General Assembly, Seoul, Republic of Korea, October 2008).

Results

A total of 109 patients were assessed at discharge/follow-up (approximately 4 weeks), of which 74 (68%) were males, and mean age with standard deviation (SD) was 34.0 (12.4) years (Table 1).

A total of 100 patients (91.7 %) provided side effect data. Of these, 38% reported some level of akathisia, meaning a score of 1 or more on the UKU SERS Pat (item 2.6). The mean akathisia UKU score with standard deviation was 0.94 (0.91) as shown in Fig. 1. No difference was found between antipsychotic naïve

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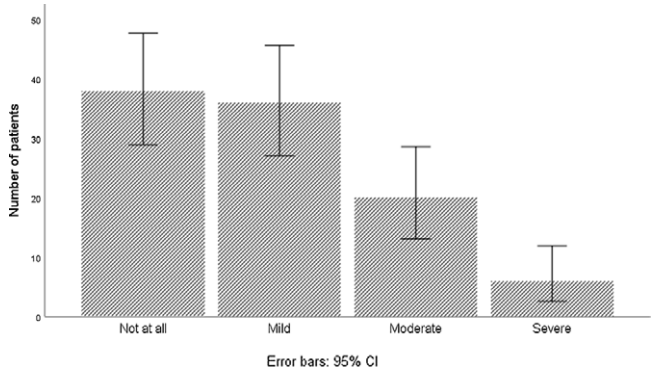

Fig. 1. Distribution of akathisia based on UKU SERS Pat item 2.6.

patients and the previously medicated, or between genders in this regard.

A Pearson correlation analysis revealed a significant and positive correlation between akathisia and severity of depression using the modified CDSS-sum score (mCDSS) (Pearson $R = 0.404$, $p < 0.001$; Spearman rho = 0.357, $p < 0.001$), and between akathisia and the suicidality item of the CDSS (Pearson $R = 0.388$, $p < 0.001$; Spearman rho = 0.394, $p < 0.001$), but not between akathisia and PANSS-EC (Pearson $R = 0.102$, $p = 0.311$; Spearman rho = 0.177, $p = 0.077$).

In a linear regression model with akathisia as the dependent variable, and mCDSS, CDSS suicidality item, PANSS-EC and Anxiety (PANSS G2) as independent variables, no statistically significant associations were found. A positive association between akathisia and suicidality was found at trend level (Beta 0.224, $p = 0.075$). The linear regression was repeated in sub-analyses in men and women separately, finding that the association between akathisia and suicidality was strengthened in men (Beta 0.306, $p = 0.048$), but not in women. In sub-analyses in those previously unexposed to antipsychotics (antipsychotic naïve patients), a positive association between akathisia and PANSS-EC was found (Beta 0.288, $p = 0.047$). In those previously exposed to antipsychotics, a positive association was found between akathisia and the mCDSS sum score (Beta 0.375, $p = 0.031$).

Discussion

The main findings of the present study were that akathisia is still a prevalent side effect in a clinically relevant sample of patients treated with AAPs. We found that akathisia was associated with suicidality, agitation and depression, although with different associations in different sub-groups. A clinically important finding was that of an association between akathisia and agitation in the antipsychotic naïve group.

We assessed the first weeks corresponding to the acute phase of antipsychotic treatment as this is the critical period for the onset of acute akathisia (Juncal-Ruiz *et al.*, 2017). The time frame is consistent with results from The European First Episode Schizophrenia Trial (EUFEST) that found akathisia to be most prevalent after the first month of antipsychotic treatment and gradually decrease thereafter (Rybakowski *et al.*, 2014). Recent reviews (Chow *et al.*, 2020; Musco *et al.*, 2020) find akathisia rates up to 27%. In our study, the incident rate was somewhat higher, with about 40% of the patients reporting some level of akathisia; however, the majority of them presented mild symptoms.

Interpreting incident rates and prevalence estimates reported across research literature is challenging due to several methodological heterogeneities and the existence of various forms of antipsychotic-induced akathisia (Barnes & Braude, 1985; Poyurovsky & Weizman, 2020). Different rating scales used for assessing extrapyramidal symptoms do not discriminate clearly between the different types of movement disorders (Martino *et al.*, 2018). Further complicating research interpretation is the lack of a universally agreed definition of the condition (Hansen, 2001), together with possible underreporting due to the subjective discomfort of akathisia that may be difficult for patients to describe (Hansen, 2001; Lohr *et al.*, 2015). The intensity of akathisia may fluctuate over the course of a day; in our study, all patients were assessed at the same time of the day, around 11.00 am. Further, the incidence rate in our study is derived from subjective reports on scale-defined akathisia and not from spontaneous verbal reporting (Demyttenaere *et al.*, 2019), and accordingly the rate is not expected to be underestimated.

The antipsychotics in our study were used in therapeutic dosages as previously reported (Johnsen *et al.*, 2010). We found no difference between the antipsychotic naïve patients, the earlier medicated ones, or gender with respect to the mean akathisia score. As our use of the term antipsychotic naïve patients can be used as a proxy for first-episode patients, one could thereby expect higher akathisia score in this group considering that previously untreated adolescents and FEP's are particularly vulnerable to develop akathisia (Kane *et al.*, 2009; Poyurovsky & Weizman, 2020; Yoshimura *et al.*, 2019). With regards to the lack of difference between gender, it has been hypothesized that women report side effects more often than men because they tolerate them less well (Seeman, 2020), though this seems not to be applicable to our study.

We used the PANSS-EC (Lindenmayer *et al.*, 2004) to measure agitation. This commonly used rating scale has been validated with excellent results (Citrome & Volavka, 2014; Montoya *et al.*, 2011), and our results in this regard are therefore expected to be valid. Previous research and case reports have suggested akathisia as a potential risk factor for violent behaviour and agitation (Cem Atbasoglu *et al.*, 2001; Salem *et al.*, 2017). Our findings do, however, not support a general association between agitation and akathisia, but importantly we found a positive association in antipsychotic naïve patients. Antipsychotic naïve patients are more sensitive to antipsychotic side effects than chronically ill patients (Hasan *et al.*, 2012). The subjective restlessness and dysphoria characterising akathisia is painful and mentally distressing. Pain is also a factor that can contribute to agitation in patients with psychosis (Marco & Vaughan, 2005). Taken together, it is important to always include akathisia as a possible differential diagnosis when new motor or psychiatric symptoms resembling anxiety emerge during antipsychotic treatment (Musco *et al.*, 2020). Both in order to treat the condition effectively and also as a means to reduce agitation in those with early-phase psychosis, a group that has increased risk of violence (Nielssen *et al.*, 2012).

We found significant associations between akathisia, suicidality and depression, respectively, although with different profiles in sub-groups. Over the years, researchers have tried to establish a firm relationship between akathisia and suicidality (Cem Atbasoglu *et al.*, 2001; Hansen, 2001; Hansen *et al.*, 2004; Hansen & Kingdom, 2006; Padder *et al.*, 2006; Reutfors *et al.*, 2016; Seemuller *et al.*, 2012). However, the magnitude of suicidal risk is hard to establish due to the sporadic nature of the event and

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heterogeneities in and across various studies (Aguilar & Siris, 2007). Albeit a unequivocal relationship between akathisia and suicidality is hard to establish, the possibility must not be excluded (Hansen, 2001). Our moderate association between akathisia and suicidality appears consistent with previous findings pointing towards a positive relationship between the two (Hansen, 2001; Reutfors *et al.*, 2016; Seemuller *et al.*, 2012). Our sub-analysis revealed a strengthened association for men in this regard. To our knowledge, this association has not been established in previous studies. As suicide prediction may be more difficult in men, together with the notion that they have higher suicide risk (Brådvik, 2018), vigilance may be called for when akathisia symptoms develops in men. Akathisia may have different impact on patients at different stages of illness and according to the duration of treatment (Hansen & Kingdom, 2006), as associations between akathisia and suicidality seem to be strongest in first episode and young patients compared to in treatment resistance (Seemuller *et al.*, 2012). Akathisia may lead to medication non-adherence (Velligan *et al.*, 2017) subsequent worsening of psychotic symptoms, increased suicidality and re-hospitalization (Musco *et al.*, 2019). Consequently, it seems plausible to suggest that early emerging akathisia may be associated with a more complicating treatment course and possibly also a poorer prognosis.

Suicidal ideation has been known to fluctuate in time (Kleiman *et al.*, 2017), especially during the early stages of schizophrenia, where limited suicidal ideation may quickly intensify to a suicide attempt (Sher & Kahn, 2019). Depression is identified as a risk factor for suicidal behaviour during the course of schizophrenia (Tandon, 2005), extra attention may thus be required for patients with akathisia and comorbid depression. According to Poyurovsky (2010), an inter-correlation between akathisia, depressive symptoms and impulsiveness may account for suicidal and violent behaviour in patients with akathisia. Taken together, the relationship between akathisia and suicidality is highly relevant and may be mutually reinforced. The positive association we found between akathisia and depression among the previously antipsychotic exposed might reflect that awareness of long-term consequences of schizophrenia may induce feelings of hopelessness. Thus, it is of clinical importance to identify and treat both anxiety and depression at an early time point.

Strength and limitations

The major strength of this study is its naturalistic prospective design integrated in clinical practice with patients consecutively recruited from psychiatric emergency wards. The sample is representative of a diverse population suffering from psychosis (Kane *et al.*, 2009; Leucht *et al.*, 2013). Patients with a history of suboptimal response to antipsychotics were not excluded, nor patients with substance abuse.

There are limitations to this study that should be considered when interpreting the results. Patients with manic psychosis or other behavioral or mental problems resulting in inability to cooperate with assessments, including organic brain disorders (dementia), agitation, hostility or pronounced suspiciousness towards the assessor, inability to use oral antipsychotics or already medicated with clozapine upon admittance, history of head injury or mental retardation, or being candidates for electroconvulsive therapy, were excluded. These represent the most gravely ill patients with psychosis, and accordingly our results cannot be generalized to, for example, patients in need of depot formulations of the APs or those with treatment resistance towards first-line agents.

Primarily, our results are based on exploratory analyses of cross-sectional data. Analyses of causality are therefore not possible. However, our findings should be used for hypothesis generation and be put on trial in prospective, hypothesis-driven longitudinal studies sufficiently powered to capture aspects of causality as well as differential associations in different subpopulations with akathisia. From a methodological point of view, the assessment of akathisia was limited to subjective sensations reported by one single item of the UKU-SERS Pat. A thorough assessment with a more comprehensive inventory such as the Barnes Akathisia Rating Scale (Barnes, 1989) would have provided more detailed information about severity, frequency and impact, this was however, beyond the scope of this study. The suicidality assessments were based solely on one item in the CDSS scale. The inclusion of supplementary or more comprehensive inventory for measuring symptomatology of suicidality would have qualified this complex area and relation to akathisia and hence likely added more clinical value to the study. Finally, there is always the possibility of residual confounding from other factors not included in our analyses. Illicit drug use can potentially be an example of such a factor, but we do not expect this to have influential impact on our results as there were relatively few patients with illicit drug use in our sample. Understanding the relationship between akathisia and depression, suicidality and agitation can be helpful in order to identify early warning signs and prevent potentially fatal outcomes. Thus further investigations in large samples are warranted, preferably in studies with special focus on how individuals with psychosis experience antipsychotic-induced side effects and the interplay between side effects and quality of life.

Our results show that also in treatment periods with AAPs akathisia is a prevalent side effect significantly associated with depression, suicidality and agitation. One should still be aware of the probability of diagnostic overlap between akathisia and agitation. It seems reasonable to believe that a reduction of akathisia could alleviate dysphoric distress. Akathisia as a side-effect should, therefore, be highlighted, and always be assessed for when a patient is treated with APs. It is important to inform the patient thoroughly about the possibility of this particular side effect when starting AP treatment. Furthermore, due actions should be undertaken to combat this troublesome side effect when present. Screening protocols for several other antipsychotic-induced side effects already exists; therefore, one should routinely screen and monitor all patients assigned to antipsychotics for movement disorders with a validated tool. Appropriate prevention and early management of side effects like akathisia may enhance the net benefits of antipsychotics.

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