Movement disorders and chronic psychosis

Five new things

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Abstract

Purpose of review: To discuss selected peer-reviewed research articles published between 2014 and 2016 and highlight 5 clinically relevant messages related to hyperkinetic and hypokinetic movement disorders in patients with chronic psychosis. **Recent findings:** A recent population-based study complemented data from clinical trials in showing increased risk of developing extrapyramidal symptoms with antipsychotic use. A community service-based longitudinal study showed that dopamine transporter imaging could help identify subgroups of patients with parkinsonism associated with antipsychotics with a progressive course, potentially manageable with L-dopa. Data from recent noteworthy clinical trials showed that a new VMAT-2 inhibitor and, for pharmacologically refractory tardive dyskinesia, deep brain stimulation of the globus pallidus internus are promising interventions. Finally, a population-based study has confirmed that hyperkinesias (encompassing chorea, dystonia, and stereotypies) may be early predictors of psychosis even in childhood and adolescence. **Summary:** Movement disorders associated with new-generation antipsychotics, including widely used agents (e.g., aripiprazole), are not rare occurrences. Better monitoring is needed to assess their true effect on patients' quality of life and functioning and to prevent underascertainment. *Neurol Clin Pract* 2017;7:163-169

Hypokinetic and hyperkinetic movement disorders in patients with psychosis are classically linked to antipsychotic use. Acute and delayed-onset (tardive) movement disorders are believed to result from, respectively, the blockage or super-sensitization of dopamine receptors along nigrostriatal and mesocortical dopaminergic pathways. Tardive involuntary movements have also been associated with maladaptive plastic rearrangements of the inferior frontal cortex, highly connected to deep subcortical nuclei and modulating motor output selection.

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Newer antipsychotic agents are generally acknowledged as safer than older ones with respect to motor side effects. However, the widespread subdivision of antipsychotic drugs into first- and second/third-generation agents may not reflect true differences in frequency of drug-induced movement disorders between these 2 groups. An important meta-analysis of randomized controlled trials showed that first- and second/third-generation antipsychotics are not truly separate for their acute motor side effect profile, with the only exception being represented by clozapine.¹ Five new-generation drugs (ziprasidone, paliperidone, risperidone, lurasidone, and zotepine) were associated with significantly more movement disorders than placebo, with odds ratios ranging between 1.61 and 3.01.¹ Moreover, previous research has also documented that the frequency of movement disorders does not translate into a gain in cost-effectiveness for newer antipsychotic drugs compared to older agents.² Replacing the umbrella term extrapyramidal symptoms with more specific designations (e.g., parkinsonism, dystonia, chorea, akathisia, stereotypies, and others) would help clarify their pathophysiologic heterogeneity in the setting of chronic psychosis, and subsequently influence management approach. The articles discussed in our review represent novel findings advancing our knowledge of this complex clinical topic.

Movement disorders associated with new antipsychotics: Are we underestimating them?

Randomized clinical trials indicate that iatrogenic movement disorders associated with newer antipsychotics are far from being a negligible clinical finding. Service- and population-based observational studies may extend the information derived from clinical trials, providing a more naturalistic estimate of the frequency of these phenomena. This may be important for antipsychotic drugs like aripiprazole, whose unique pharmacodynamic profile combining partial agonistic and antagonistic properties on D2 dopamine receptors has contributed to its widespread use. Clinical trial data did not demonstrate a significantly higher risk of movement disorders with aripiprazole compared to placebo.¹ As field experience increased, however, several case reports appeared that documented parkinsonism or dyskinesia linked to aripiprazole. A recent, useful addition to the literature on aripiprazole has come from a nested case-control study³ that used a large health claims database composed of a population of 6,110,723 patients aged 15–60 years who had received at least one drug prescription during the previous 8 years; the authors excluded from both case and control samples all the patients who had received a diagnosis of Parkinson disease, bipolar disorder, or schizophrenia before the event of interest (i.e., first prescription of aripiprazole), in order to prevent confounding from previous exposure to dopamine-modulating agents.³ The likelihood of developing any movement disorder was 5.38 times higher among aripiprazole users. This was mainly determined by acute/subacute movement disorders, as the highest likelihood was observed in those who had taken a single prescription, with a mean time from first prescription to first movement disorder (any type) of 63 days. Dyskinesias (usually indicating chorea or dystonia, or a combination) were 8.5 times more common among aripiprazole users. No significant difference in movement disorders risk was observed between aripiprazole and risperidone; given the relatively high risk of risperidone to generate tardive dyskinesia, this finding could reflect limited power of this study in estimating delayed-onset movement disorders with aripiprazole. Notwithstanding the limitations of analyses of health claims databases, e.g., lack of direct verification of diagnoses, these findings show that the movement disorders risk following even a single administration of aripiprazole is not trivial and comparable to that of other new-generation antipsychotics. Consistent with this study, a recent community-based cohort study reported a 27% incidence of parkinsonism with aripiprazole.⁴ The above findings are also coherent with 2 recent meta-analyses. A first meta-analysis of clinical trials measured the relative risk of akathisia with aripiprazole compared to placebo, demonstrating a 1.52-fold higher risk of causing akathisia, which was statistically significant.⁵ Interestingly, in the same study, other third-generation antipsychotics like lurasidone and asenapine exhibited an even

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higher relative risk of akathisia. A second meta-analysis of the literature on children and adolescents has reported a mean 17.5% incidence of acute movement disorders (encompassing parkinsonism, tremor, dystonia, and akathisia) following first use of aripiprazole.⁶

Characterizing antipsychotic-associated parkinsonism: Can this guide treatment decisions?

Parkinsonism associated with psychosis and antipsychotics exposure is often simplistically labeled as drug-induced. However, parkinsonism does not always improve after discontinuation of the potentially offending drug, and may even worsen over time. Moreover, a presynaptic striatal dopaminergic deficit on dopamine transporter (DAT) SPECT was observed in 42% of patients with schizophrenia, similarly to patients with degenerative parkinsonism.⁷ A 2-year longitudinal study on 60 patients with schizophrenia and parkinsonism associated with antipsychotics compared the clinical outcome of those with normal and abnormal DAT SPECT at baseline.⁸ Patients with abnormal DAT SPECT manifested progression of motor disability, with a proportion of them improving on L-dopa. These findings point towards a heterogeneous pathophysiology of antipsychotics-associated parkinsonism, which might be underlined by at least 2 main mechanisms: (1) postsynaptic blockage of D2 receptors by chronic antipsychotic treatment in patients with normal SPECT without evidence of disease progression at follow-up and with lack of response to L-dopa; (2) denervation of the nigrostriatal pathway over the course of chronic antipsychotic treatment in patients with abnormal SPECT and response to L-dopa.

These data do not provide any insight on the mechanism leading to nigrostriatal damage in patients with schizophrenia chronically exposed to antipsychotics. A direct neurotoxic effect of long-term antipsychotic treatment can be hypothesized, as in vitro studies show increase in oxidative stress⁹ and blockage of autophagolysosome formation¹⁰ by antipsychotics. A degenerative parkinsonism during the course of psychosis should also be considered; for example, a common genetic risk factor for schizophrenia, the 22q11.2 deletion syndrome, is associated with the risk of development of early-onset Parkinson disease (PD) with variable neuropathology.¹¹ This possibility is further suggested by a study reporting 2 patients treated with antipsychotics in whom parkinsonian features subsided after stopping antipsychotics and who had autopsy findings consistent with PD.¹²

A preliminary clinical message of this study is that abnormal DAT SPECT may predict the usefulness of L-dopa in these patients. L-dopa treatment was tolerated, but caution is needed due to small sample size and short treatment duration.⁸ Larger, randomized controlled trials of L-dopa in patients with stable psychosis and parkinsonism are necessary to confirm safety and efficacy.

Progress in monoamine transport inhibition as a treatment target in tardive movement disorders

The management of tardive dyskinesia (TD) entails complex risk/benefit calculations in evaluating strategies like antipsychotic dose reduction or switch to compounds with lower D2 blockage potency. When adjustments to antipsychotic treatment are not deemed safe,

Hyperkinetic disorders are frequent in individuals at clinically high risk of psychosis as well as at first psychotic episode.

add-on pharmacotherapies are considered, despite lack of high quality evidence (see references 13 and 14 for comprehensive reviews). Tetrabenazine, a vesicle monoamine transporter-2 (VMAT2) inhibitor used off-label in the United States and approved in some EU countries, appears to be a promising add-on, but its use is hindered by relatively short half-life. A recent phase IIb study has shown efficacy and tolerability of NBI-98854 (valbenazine) in the treatment of severe TD in patients with schizophrenia/schizoaffective disorder and mood and gastrointestinal disorders.¹⁵ Like tetrabenazine, valbenazine is converted to (+)- α -dihydrotetrabenazine, a selective VMAT2 inhibitor, has a longer half-life allowing a more acceptable once-daily administration, and lacks the mild D2 antagonistic effect exerted by another tetrabenazine metabolite.¹⁶ In this 6-week duration trial, 102 patients were randomized to valbenazine (open 4-week titration from 25 to 75 mg) or placebo. In the modified intention-to-treat cohort, valbenazine was markedly (>30%) superior to placebo in reducing TD severity, rated by movement disorders specialists through centralized video-based assessment. This short-term treatment with valbenazine was well-tolerated, and side effects included fatigue and headache in <10% of patients. A phase III trial is underway and the Food and Drug Administration has granted breakthrough status to valbenazine for TD treatment, minimizing approval hurdles if the larger trial is successful.¹⁷

Increasing evidence for deep brain stimulation in TD

A large proportion of patients with TD (~10%) remain severely disabled even after pharmacologic treatment.¹⁸ Alternative approaches include deep brain stimulation (DBS) of the globus pallidus internus, found promising in earlier case reports¹⁹ and in a 6-month, prospective, phase 2 double-blind multicenter study of 10 patients with TD.²⁰ A longer-term follow-up study from the same network reported on a larger sample (n = 19), evaluated blindly at 6 months and in open-label at 12 months; additional long-term data after 4–11 years of follow-up on a subset of 14 of the 19 patients was also provided.²¹ The study demonstrates long-term efficacy and safety of pallidal neurostimulation in patients with TD, using the Extrapyramidal Symptoms Rating Scale (ESRS) as primary outcome measure. All subscores of ESRS, including parkinsonism, were still improved at 1-year follow-up; half of the patients could discontinue antidyskinetic drugs. The severity of psychiatric symptoms required safe stabilization before DBS. Importantly, cognitive and psychiatric safety of DBS in TD was very promising: depression and psychiatric symptoms did not change in severity after DBS in the majority of patients, and psychiatric exacerbations in 8 patients were managed successfully by adjusting medications or psychotherapy, without need for stimulation withdrawal. Despite these promising data on efficacy and safety, the risk for adverse effects linked to the surgical procedure and device (infections, malpositioning) as well to the stimulation itself (dysarthria, balance and gait disturbances) requires high compliance from patients and caregivers, and careful long-term monitoring by an expert multidisciplinary team.

Do movement disorders in drug-naïve high-risk individuals help predict psychosis?

Involuntary movements have been reported in 9%–17% of antipsychotic-naïve patients with schizophrenia.²² Hyperkinetic disorders are frequent in individuals at clinically high risk (CHR) of psychosis as well as at first psychotic episode, potentially reflecting striatal pathology and predicting poorer cognitive and psychosocial functioning.^{23,24} These potential predictors might already be present very early in life. A Swiss study²⁵ has screened a sex-stratified sample of 102

youth aged 8–17 years, randomly selected from the general population of the Canton Bern, for CHR criteria based on attenuated and brief intermittent psychotic symptoms (present in 10.8%), as well as hyperkinesias using the Abnormal Involuntary Movement Scale (AIMS; score ≥ 2 in 12.7%), psychosocial functioning, verbal memory/learning, and axis I comorbidities. The AIMS scale captures a spectrum of hyperkinesias encompassing chorea, dystonia, and stereotypies, with the important limitation of not distinguishing between them. In this study,²⁵ the frequency of hyperkinesias increased significantly from people without any CHR symptom (4 of 66, 6.1%) to those with CHR symptoms but not fulfilling CHR criteria (4 of 25, 16%) to those fulfilling CHR criteria (5 of 11, 45.5%). Moreover, poorer social and occupational functioning was observed in youth with abnormal involuntary movements. This study provides unprecedented population-based evidence supporting the association of hyperkinesias with higher risk for psychosis already from childhood/adolescent years, consistent with a neurodevelopmental link between psychosis and abnormal motor output.²⁶ Evaluating hyperkinesias might, therefore, represent an easily accessible predictor of psychosis. Future research should clarify which specific hyperkinesias are the strongest predictors.

CONCLUSION

Movement disorders in the setting of chronic psychosis remain an important clinical problem, worthy of the attention of clinicians and researchers. Several open questions should be addressed by future research. New observational studies describing the long-term outcome of movement disorders associated with antipsychotics, especially parkinsonism, would help guide management and direct prevention. Future research should also assess the advantage of using antipsychotic compounds with different mechanism of action, like selective serotonin receptor agonists and antagonists (e.g., pimavan-serin, vabicaserin, ondansetron).²⁷ Pragmatic treatment guidelines for movement disorders associated with antipsychotics remain an unmet need. Finally, we look forward to the development of valid and reliable screening tools in drug-naïve patients and high-risk individuals to guide early treatment and facilitate early diagnosis of psychotic syndromes.

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- Movement disorders associated with new-generation antipsychotics are not rare. Better monitoring is needed to assess their true effect on patients' quality of life and functioning and to prevent underascertainment.
- Parkinsonism associated with antipsychotics is clinically and pathologically heterogeneous. DAT SPECT might help identify patients at risk of progression. More research is needed to clarify efficacy and safety of L-dopa in a subgroup of these patients.
- Valbenazine, a new VMAT2 inhibitor, appears to be promising for the treatment of severe TD.
- DBS of the globus pallidus internus showed potential efficacy and safety in the treatment of severe, pharmacoresistant TD.
- Hyperkinetic movement disorders are an early clinical feature in almost half of patients with attenuated and brief intermittent psychotic symptoms, who are at clinically high risk of psychosis.

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