Agitation in schizophrenia: origins and evidence-based treatment

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Purpose of review
Agitation associated with schizophrenia remains an important clinical concern and if not managed effectively, can escalate into aggressive behavior. This is a review of the recent biomedical literature on agitation in individuals with schizophrenia.

Recent findings
Themes in the recent literature include consideration of comorbidities such as cigarette smoking and cannabis use. Surveys reveal that pharmacological approaches to manage agitation have changed little, with haloperidol remaining in common use and intramuscular administration of antipsychotics and/or benzodiazepines being frequently administered to more severely agitated/aggressive individuals. Of note, ketamine has been recently adopted for use in severe agitation in medical emergency departments, but the risk of this medication for people with schizophrenia is unclear. At present, inhaled loxapine remains the only rapidly acting noninjectable FDA-approved treatment for agitation associated with schizophrenia. In development is an intranasal formulation for olanzapine (a well characterized atypical antipsychotic already approved to treat agitation) and a sublingual film for dexmedetomidine (an α2-adrenergic agonist used as an anesthetic and now being repurposed).

Summary
Comorbidities can contribute to agitation and can make an accurate differential diagnosis challenging. The ongoing development of rapidly acting novel formulations of antiagitation medications, if successful, may facilitate clinical treatment by providing additional options.

Keywords
agitation, antipsychotics, cannabis, catatonia, schizophrenia

INTRODUCTION

Agitation in individuals with schizophrenia is commonly associated with exacerbations of psychotic symptoms but can also manifest itself in the presence of poor impulse control, and when unchecked, can escalate towards aggression and violence [1,2]. Causal pathways have also implicated substance abuse and antisocial personality/psychopathy in this process [2]. Phenomenologically, agitation is a heterogenous syndrome encompassing symptoms of restlessness, irritability, anxiety, and increased or excessive movement or speech that lacks specific purpose [3,4]. Risk factors for aggressive behaviors in agitated patients include behavioral warning signs such as hostile mood and verbal threats, prior history of aggression, younger age, male sex, and as noted, substance abuse [5]. Although nonpharmacological de-escalation strategies are advocated to manage agitation [6], medications are also often required [7]. The scope of this review is to appraise the recent published biomedical literature on agitation in people with schizophrenia.

METHODS

The current review is based on a literature search using the US National Library of Medicine PubMed.gov resource (https://pubmed.ncbi.nlm.nih.gov/) using the search string '(''schizophrenia'' AND ''agitation'') OR (schizophrenia AND agitation)' for any articles published from 1 June 2019 to 17 November 2020. The titles and abstracts of 43

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KEY POINTS

- In one study, smokers had a greater number of anxiety/agitation episodes and utilized as-needed medications at a higher frequency compared with nonsmokers.
- Despite the availability of several second-generation antipsychotics specifically studied in agitated individuals with schizophrenia, use of haloperidol remains common.
- Development is ongoing for noninjectable routes of medication administration; already available is an inhaled formulation of loxapine, and in clinical development are an intranasal device for administering olanzapine and a sublingual film of dexmedetomidine.

unique listings were screened for relevance, of which two were published in a language other than English and one was retracted, leaving 40 entries. Excluded from further consideration were broad reviews that were not focused on agitation in schizophrenia, studies that describe a laboratory analytical technique in the absence of human data (e.g., quantification of medication blood levels using chromatography-spectrometry), or studies where schizophrenia was an exclusion criterion. A total of 19 articles were found that provided information on agitation in individuals with schizophrenia. Topics included the impact of comorbidities, including considerations regarding inflammatory response, older populations, available treatments, and medications in development. Additional citations were gathered from the reference lists from the selected articles, as well as from the author's personal file library.

COMORBIDITIES: FROM SMOKING CIGARETTES AND CANNABIS TO ACUTE SARS-CoV-2 INFECTION, AND A ROLE FOR THE INFLAMMATORY RESPONSE

Cigarette smoking is perhaps the most common comorbidity associated with schizophrenia, with an estimated prevalence rate of 60–90% [8]. In a retrospective chart review conducted in 2010 and reported in 2019, 38 in-patients with schizophrenia in a long-term psychiatric facility were assessed regarding their smoking status and the occurrence of anxiety, agitation, and utilization of as-needed medications [9▪]. Smokers had a greater number of anxiety episodes and utilized as-needed medications at a higher frequency compared with nonsmokers for the relief of anxiety and agitation symptoms. It is not known if this is related to changes in the amount of smoking over time, potential nicotine withdrawal, induction of the metabolism of certain antipsychotics, or psychosocial factors related to the obtaining and smoking of cigarettes within an institution. Because smoking is now generally restricted in hospitals, newly admitted in-patients who are heavy smokers often require nicotine replacement. An older double-blind, randomized, placebo-controlled study demonstrated a strong effect of nicotine replacement therapy for the reduction of agitation and aggression in smokers with schizophrenia [10]. Smoking status should be routinely ascertained in persons with schizophrenia, both as a marker for potential anxiety or agitation, as well as foreseeing the potential consequences of restricting cigarette use.

Cannabis use is also common in people with schizophrenia, with an estimated prevalence rate of about 26% [11]. In addition to the observation that cannabis abuse is associated with medication nonadherence [12], catatonia has also been reported [13▪] which can cause substantial diagnostic confusion with psychomotor signs that range from stupor to agitation [14▪▪], and is considered a neurological emergency [15].

Some of the biological research regarding the effects of cannabis on the brain in psychotic patients has focused on the role of IL-6, an inflammatory cytokine [16▪▪]. In one study conducted among 119 patients admitted to a psychiatric unit with acute psychosis, individuals who had toxicology positive for natural and/or synthetic cannabinoids were compared with patients with negative cannabinoid toxicology [16▪▪]. Although psychosis severity was similar between groups, cannabinoid-positive participants were more likely to receive as-needed medications for agitation in the psychiatric emergency room. Among cannabinoid-positive participants, IL-6 levels negatively correlated with measures of psychopathology. In general, substance use has been associated with increased levels of impulsivity and psychomotor agitation, rendering this comorbidity an important diagnostic conundrum [17]; examining inflammatory cytokines adds a new dimension to exploring the relationship between exogenous factors and agitated behavior.

The role of the inflammatory response regarding agitation was also examined in a study of the impact of air pollution [18▪]. This was a community-based cohort study in China that enrolled 58 people with schizophrenia who were followed up every 2 weeks during the period of August 2018 to June 2019. Exposure to particulate matter with an aerodynamic diameter less than 2.5 μm was statistically related to anxiety/agitation (as well as depression/withdrawal, initial psychosis, and disinhibition). The inflammatory cytokine IL-17 was identified as a possible intermediary.

As the world navigates the current public health emergency regarding SARS-CoV-2 infection, agitation can be seen in these patients, as enumerated by a consultation-liaison psychiatry team in Qatar [19▪]. Among the 50 patients included in the study, agitation was reported in 25 (50%) of the sample. Although only three (6%) had a past psychiatric history of schizophrenia, nine (18%) were diagnosed as nonaffective psychosis by the consultation-liaison team. Correlation of levels of inflammatory cytokines and agitation in patients with schizophrenia and SARS-CoV-2 infection remains to be studied.

Agitation in a person previously diagnosed with schizophrenia but now not responding to antipsychotics requires a thorough work-up. A case report of a 28-year-old male with anti-N-Methyl-D-aspartate (NMDA) receptor encephalitis illustrates this point [20▪]. The presence of agitation as part of catatonia in patients with anti-NMDA receptor encephalitis is further described in a series of 58 patients from the Institute of Neurology and Neurosurgery of Mexico [21]. In that report, the authors concluded that catatonic syndrome is a frequent feature in patients with anti-NMDA receptor encephalitis, and that the pattern of delirium, psychomotor agitation, and hallucinations can be a source of diagnostic and therapeutic errors, as most physicians associate catatonia with schizophrenia and affective disorders.

OLDER POPULATIONS

Although risk factors for aggressive behaviors in agitated patients include younger age [5], older people with schizophrenia can exhibit these behaviors as well. This was explored among 126 residents (half with schizophrenia spectrum disorder) at several nursing homes in The Netherlands [22▪] using the Cohen Mansfield Agitation Inventory to measure agitation/aggression. Mean age was 67 years. A counterintuitive finding was a correlation between physical aggression and higher observed psychological well being. It was thought that disinhibition, also related to higher observed psychological well being, served as an intermediary. The results are not subcategorized by diagnosis, and it is not known if these relationships would remain true if only patients with schizophrenia were to be analyzed. Agitation in older individuals with schizophrenia is a relatively understudied topic compared with work being done in dementia-related agitation, where a query of the PubMed.gov resource using the search string '(''dementia'' AND ''agitation'') OR (dementia AND agitation)' for any articles published from 1 June 2019 to 17 November 2020, provided 276 results; this is over six-fold larger than the number of results for searching on schizophrenia and agitation regardless of the age group studied.

WHAT IS USED TO MANAGE AGITATION IN SCHIZOPHRENIA?

The use of first-generation antipsychotics (such as intramuscular haloperidol) to manage agitation remains common [23▪▪] even though second-generation antipsychotics such ziprasidone or olanzapine (also available as short-acting intramuscular formulations) may be more suitable as they are better tolerated and are at least equally efficacious [5,7,24–26].

In a multicenter, observational study in 14 psychiatry hospitals in China, among 847 newly hospitalized patients with schizophrenia meeting criteria for agitation based on a rating scale, all were prescribed one or more antipsychotics in the first 2 weeks of hospitalization and 40 (4.7%) were also prescribed a benzodiazepine [23▪▪]. The most used antipsychotic was haloperidol, identified in 302 patients (36%, and all but two patients receiving the intramuscular formulation), followed by olanzapine in 276 (33%) and risperidone in 258 (30%). Polypharmacy was more likely used for severe agitation. Of note, 81 patients (9.5%) were also treated with modified electroconvulsive therapy, a treatment that remains recommended for patients with schizophrenia who have severe agitation, and to manage catatonia, suicidal behavior, or clozapine-resistant schizophrenia [27▪]. The relatively high utilization of haloperidol is consistent with data reported from a psychiatric emergency department (ED) located at an academic medical center in California [28] where in 2014 among 388 acutely agitated patients who were administered an antipsychotic medication, intramuscular haloperidol was given as the initial antipsychotic in 298 cases (77%); the authors explain that there were formulary restrictions from using alternatives. Other investigators have also observed that haloperidol continues to be used, despite expert recommendations to use newer agents [29].

In a study of physical assaults using incident reports and electronic medical records from one psychiatric emergency room and two inpatient psychiatric units over a 5-year period, there were 60 incidents in the psychiatric emergency room and 124 incidents on the inpatient units [30▪]. Diagnoses of schizophrenia, schizoaffective, and bipolar disorder were analyzed as a group. Twenty antecedent themes were identified as precipitating factors, organized into four major categories: psychosis, conflict with peers (e.g., taunting), conflicts with staff (e.g., admission or discharge dispute), and other themes

(e.g., family involvement). The most common precipitants were related to psychosis, but conflicts with peers and staff were also frequently reported. Intramuscular antipsychotics were the medications used most often (about 70%) followed by intramuscular benzodiazepines (35%), with oral antipsychotics and oral benzodiazepines utilization close to 20% each; percentages add up to more than 100% implying that a combination approach was sometimes used. The specific agents administered were not reported. The relatively high rate of intramuscular injection use likely reflects the severity of the incidents being managed (physical assault).

Ketamine is an emerging medication being used to manage severe agitation in medical ED settings [31]; however, its use in individuals with schizophrenia may lead to worsening of psychosis [32]. A retrospective cohort study was conducted at two urban tertiary academic medical center EDs, utilizing chart review of patients requiring prehospital sedation for severe agitation, and included individuals with schizophrenia [33▪]. Patients received either parenteral ketamine or parenteral benzodiazepine. Although the authors of the report concluded that administration of prehospital ketamine for severe agitation was not associated with an increase in the rate of psychiatric evaluation in the ED or psychiatric inpatient admission when compared with benzodiazepine treatment, the sample size consisted of only 15 individuals with schizophrenia out of the total study sample of 134 (141 encounters). Among the 16 encounters with individuals with schizophrenia, 10 of the visits involved the use of a benzodiazepine and six the use of ketamine. One patient in each cohort had an inpatient psychiatric admission.

Some of the second-generation antipsychotics have demonstrated specific antihostility effects in individuals with schizophrenia, which in turn may predict their effects regarding aggression [34▪]. Some of the work has involved examining both agitation and hostility separately as was done in a post-hoc analysis of short-term and long-term studies of brexpiprazole on agitation and hostility in patients with schizophrenia [35▪]. In the short-term studies, 1094 patients received placebo, 2 mg/day of brexpiprazole, or 4 mg/day of brexpiprazole; 346 brexpiprazole-treated patients rolled over into the long-term study and received 1–4 mg/day of brexpiprazole. In the 6-week acute studies, brexpiprazole was superior to placebo on measures of agitation, with a possible dose response, and with benefits maintained during the open-label 1-year extension. Brexpiprazole is not available as an intramuscular medication. Acute (2–24 h) efficacy on agitation was not studied.

Inhaled loxapine remains available as a fast-acting intervention to manage agitation associated with schizophrenia, as reviewed in an article examining its safety, efficacy, and acceptability to patients [36▪]. This is not a new intervention, having been approved by the US FDA in 2012, but because of cost and restrictions on use due to a Risk Evaluation and Mitigation Strategy program focused on pulmonary monitoring, it has not been widely adopted. The review notes that efficacy in reducing agitation was evidenced as early as 10 min after administration (the first time point measured) with both the 5 and 10 mg dose strengths. Number needed to treat to achieve response versus placebo at 2 h post administration was similar to that observed for intramuscular preparations of ziprasidone, olanzapine, haloperidol, and aripiprazole. Dysgeusia is the most common adverse effect, with rates of 14.3, 11.3, and 4.9% for loxapine 10, 5 mg, and placebo, respectively. Patient acceptability using the one-time use device was favorable.

There remains a need to systematically evaluate all current options to treat agitation in psychosis. A study protocol for a systematic review and network meta-analysis for this purpose has been published [37▪▪], and its completion is eagerly anticipated.

WHAT NEW PHARMACOLOGICAL AGENTS ARE BEING DEVELOPED?

Published was a review that summarized two investigational agents in clinical development for the management of acute agitation in patients with schizophrenia: intranasal olanzapine and dexmedetomidine sublingual film [38▪▪]. Olanzapine is a second-generation antipsychotic that has been well characterized over the years and is available in oral formulations (traditional tablet and orally disintegrating tablet), a short-acting intramuscular formulation, and a long-acting intramuscular formulation [39]. The intranasal formulation is administered through a device and results in rapid absorption and pharmacodynamic effects that can potentially replace the need for intramuscular injection of short-acting olanzapine [40]. However, no data is currently available on the use of intranasal olanzapine in agitated patients with schizophrenia. Olanzapine short-acting intramuscular has been associated with serious oversedation when combined with benzodiazepines, although the causal relationship underlying this association has been questioned [41]. It remains unknown how well intranasal olanzapine would be tolerated under similar conditions.

Dexmedetomidine is a relatively selective α2-adrenergic agonist originally approved in 1999 as

an intravenous formulation for sedation in intubated and ventilated patients in ICUs, for periods less than 24 h [38▪▪]. Dexmedetomidine has also been used for procedural sedation in nonintubated patients, adjuvant use for analgesia, sedation in children (including intranasal and buccal routes of administration). Compared with benzodiazepines, dexmedetomidine has less impact on respiration, and patients are more easily rousable. Because dexmedetomidine has poor oral bioavailability as a result of high first-pass metabolism, a sublingual film, was developed [42]. Topline results of a randomized clinical trial in 381 individuals with schizophrenia and agitation were provided in a press release [43] and it is anticipated that more complete information will be available in poster presentations and peer reviewed publications in the near future. Two doses of the sublingual thin film of dexmedetomidine were compared versus placebo: 120 and 180 μg. In patients with schizophrenia, statistically significant and clinically meaningful reductions in agitation scores were noted at 2 h, the primary endpoint, for both the high and low-dose cohorts compared with placebo. Improvement was noted beginning as early as 20 min for the 180 μg dose level. Responder rates at 2 h post administration were close to 90% for this dose, compared with 34% for patients randomized to placebo. Similar results were noted for the analogous agitation in bipolar disorder study, and across both studies dexmedetomidine sublingual film was reasonably tolerated. Overall, the most commonly reported adverse events from both trials were somnolence (22% for 180 μg dose arms, 21% for 120 μg dose arms, and 6% for placebo arms), dry mouth (4.4, 7.5, and 1.2%, respectively), and dizziness (6.0, 3.9, and 0.8%, respectively). All adverse events were mild to moderate in severity, with none categorized as severe or requiring further intervention or monitoring. Few participants discontinued the trials due to adverse events.

CONCLUSION

A common theme in the recent literature on agitation in individuals with schizophrenia has been understanding some of the comorbidities and diagnostic challenges. The role of the inflammatory response is being explored, including regarding environmental factors such as air pollution. Agitation in older people with schizophrenia appears to get little research attention. Despite the availability of several second-generation antipsychotics specifically studied in agitated individuals with schizophrenia, use of haloperidol remains common even though alternatives may be more suitable. In progress is a systematic review and network meta-analysis to evaluate all current options to treat agitation in psychosis. In the meantime, development is ongoing for noninjectable routes of medication administration. Already available is an inhaled formulation of loxapine, and in clinical development are an intranasal device for administering olanzapine and a sublingual film of dexmedetomidine.

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