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TECHNICAL NOTE

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Neuroleptic-Induced Akathisia and Violence: A Review*

ABSTRACT: Surprisingly, the association of neuroleptic-induced akathisia and aggressive behavior was not formally recognized until nearly two and one-half decades of antipsychotic prescribing had passed. Using a search of the anglophonic literature, this phenomenon is reviewed. Advances in psychopharmacology have reduced neuroleptic-induced akathisia and hold promise to eliminate it altogether. Nonetheless, important clinical and forensic aspects of neuroleptic-induced akathisia and aggression remain and are explored.

KEYWORDS: forensic science, antipsychotics, neuroleptics, akathisia, violence, aggression

Neuroleptic or antipsychotic medication has been the mainstay of the treatment of psychotic disorders since their introduction about a half-century ago. The earlier neuroleptics, now known as typical, conventional, older generation, or first generation antipsychotics could cause a significant number of patients to experience neurologic side effects and adverse reactions. The principal acute side effects have been identified as belonging to the extrapyramidal class, which include drug-induced Parkinsonism, neuroleptic-induced akathisia (NIA), and acute dystonic reaction (1). The typical class of antipsychotics includes the following medications: chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, thiothixene, thioridazine, and trifluoperazine. The atypical or newer generation, sometimes further divided into second and third generation antipsychotics (2), has been in use for a little over a decade. One of the defining properties of these agents is the substantially reduced frequency of acute neurologic side effects encountered with their use (3). Atypical antipsychotics available in the United States include risperidone, olanzapine, quetiapine, ziprasidone, and clozapine. For this presentation we focus on the extrapyramidal side effect of NIA.

The word akathisia derives from Greek and literally translates to "not to sit" (4). Akathisia is characterized by a subjective sense of restlessness or inner agitation. Manifestations of akathisia may include fidgeting, irritability, difficulty sitting still, a compulsion to move, repetitive leg movements, muscular tension, restlessness, sleep disturbances, hyperactivity, and extreme agitation (4–6).

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Reported prevalence rates of akathisia for patients on typical neuroleptics have ranged from 12.5 to 75% (4) though the range is generally thought to be between 20 to 45% (7). For mentally retarded patients prescribed typical neuroleptics, two studies reported 7 and 13% prevalence rates (4).

To critically review the topic of akathisia-related violence, we used computerized searches via Medline and PsycInfo of the anglophonic literature (1966 to January 2002). The keywords used to map the search were akathisia and aggression and akathisia and violence. The search yielded 18 citations. Eleven of these citations were relevant for this review (4–6,8–14, 18) and form the basis for the index analysis.

Akathisia and Violence Case Reports

The first report hypothesizing a link between akathisia and violent behavior first appeared in 1978 by Keckich nearly two and one-half decades since the introduction of neuroleptic use in the United States (8). In Keckich's case, a 29–year-old man diagnosed with sociopathic personality and transvestism was treated with haloperidol only after developing psychotic symptoms from treatment with imipramine (N.B., upon re-considering the diagnosis based on the information Keckich provided, a substance use disorder might also be included). His violent behavior consisted of assaulting his dog.

Since Keckich's initial report, there have been only infrequent reportings of akathisia-associated violence (4,5,9).

Schulte presented five case reports in which three involved homicidal behaviors and two suicidal behaviors linked to haloperidol-induced akathisia as the hypothesized principal etiologic influence on the index behavior (9). Two of the homicidal cases suffered from a chronic psychotic disorder and one suffered from mild mental retardation.

Galynker and Nazarian presented a case of a 47–year-old man with bipolar disorder whose haloperidol-induced akathisia was thought to be associated with his attack on an emergency room staff

member and his subsequent destruction of ward property after admission as an inpatient (5).

Gross and colleagues presented a case of a 40–year-old woman with profound mental retardation who developed first development chlorpromazine-induced and later haloperidol-induced akathisia that was retrospectively hypothesized to have been a principal factor in her increased aggression (4).

Although very few cases of NIA-associated violence have been reported in the literature, it has been generally accepted that clinicians need to differentiate between akathisia manifesting as violence versus generalized psychotic agitation (5) and be alert to recognizing akathisia as a cause of increased irritability and violence (14).

Studies of NIA and Violence

Not only have there been few case reports of NIA-associated violence, there have been only four studies in which NIA and violence were investigated (10–13).

As part of a clozapine study that included a placebo washout period, Herrera and associates studied 16 male patients diagnosed with DSM-III schizophrenia that had proven resistant to previous neuroleptic treatment efforts (10). In a retrospective chart review, none of the 16 had any unusual history of violence. After the placebo washout period, the patients were prescribed haloperidol and this was titrated upwards with the final dose reached at six weeks. This was followed by a second placebo washout period. After this washout, they were prescribed either chlorpromazine ($\leq$1800 mg/d) or clozapine ($\leq$900 mg/day). Benztropine was used along with haloperidol or chlorpromazine to treat extrapyramidal side effects. There were significantly more violent episodes manifested during haloperidol use than during placebo or chlorpromazine. Violence was measured using Lion's Scale for Inpatient Violence (15), which tracks episodes of hostile and assaultive behavior with subscales for physical (assaults against people, property) and verbal (assaults against patients or staff). Compared to the violent group, the non-violent group exhibited a trend for a lower frequency of NIA (and other extrapyramidal side effects) during haloperidol use. However, this trend was not statistically significant.

Raja and associates studied all (N=313) patients admitted between 5/26/94 and 7/10/95 to a 12-bed psychiatric intensive care unit of a public hospital in Italy (13). Using the Barnes Akathisia scale (16), higher scores for akathisia were observed in the violent group than the hostile group, but the non-hostile group score was higher than the hostile group. Hostile behavior was associated with Brief Psychiatric Rating Scale (BPRS) psychotic factor score, BPRS hostility/agitation score, antipsychotic daily dose, and benzodiazepine daily dose.

At an Australian hospital, using the Staff Observation Aggression Scale (17), Cheung and colleagues compared 31 physically aggressive versus 31 non-aggressive DSM-III-R schizophrenics as a function of the extrapyramidal symptoms of drug-induced Parkinsonism, akathisia, and tardive dyskinesia (12). There was a non-significant increase in akathisia among the aggressive group. However, the aggressive group was statistically more likely to be prescribed high potency or a combination of high potency and low potency neuroleptics than the non-aggressive group and statistically more likely to be prescribed benzodiazepines. None of the extrapyramidal symptoms could distinguish between the two groups.

Crowner and associates studied assaultive behaviors by videotaping dayroom of a 14-bed unit of chronically violent patients at a state hospital (11). Assaults were defined as hitting kicking, slapping, punching, or throwing objects. Patients were categorized as having akathisia or not by using Barnes scale. About half of the assaults and victims had akathisia before the assaultive incident.

Discussion

The few case reports and studies (which were part of larger research studies and the findings about akathisia fell out of the larger data sets) support the observations of the case reports in regard to the association between NIA and aggression. Lowering the risk for NIA-associated aggression turns on the primary prevention of NIA. Fortunately, recent research has identified the pathophysiology of NIA as a function of mesocortical dopaminergic blockade, increased central norepinephrine antagonizing mesocortical dopamine function, low ratio of 5-HT_2 receptor to D_2 receptor blockade, and low D_1 receptor affinity (6). This model posits that treatment interventions would involve reduction of mesocortical dopaminergic blockade and reduction of central norepinephrine hyperactivity (6). This suggests the treatment strategies involving the use of beta-blockers to reduce central norepinephrine hyperactivity, the use of atypical antipsychotics with high $5HT_2$ receptor and lower dopaminergic receptor antagonism, and the use of benzodiazepines (6). In a study of 19 patients with NIA (from thiothixene, perphenazine, haloperidol, chlorpromazine, mesoridazine, fluphenazine, or trifluoperazine), treatment with benztropine or propranolol resulted in a reduction in psychopathology as measured by BPRS scores in 21.3 and 22.4%, respectively (18). Nevertheless, what is particularly telling has been the absence of any reports of NIA and violence so far in patients prescribed the newer generation neuroleptics. This would be a logical outgrowth of the reduced frequency of NIA found with the use of atypical neuroleptics and follows from the observation that these antipsychotics have a preponderance of 5-HT_{2a} receptor blockade over D_2 receptor antagonism (7).

Although NIA-associated violence has been less frequently observed with the advent of the newer generation antipsychotics, clinicians still need to maintain vigilance for this undesirable phenomenon, especially since the older generation antipsychotics remain in use because of clinical efficacy for individual patients, managed care constraints on formularies, clinician or patient preference, and the current lack of (short and long-acting) injectable forms of the atypical neuroleptics. The appearance of a rapidly dissolving pill form (olanzapine) and anticipated development of injectable forms of newer generation antipsychotics may further reduce NIA-associated violence.

Although there is an optimistic picture for the possible extinction of NIA-associated violence, we do not anticipate that this will happen in the next few years. As such, there remains the specter of NIA-associated aggression as a relevant factor when considering a criminal defendant's mental state at the time of an alleged crime. Although NIA-associated aggression may be a relevant factor, from the available research, it cannot be scientifically posited that it would be the sole factor in the genesis of aggression. Individual case reports alone lack the sufficient rigor to hypothesize at the level of reasonable medical probability that NIA would be the proximate cause of aggression. The few studies documenting NIA that were part of larger studies cannot easily differentiate NIA associated violence from the other violence associated with other risk factors, including co-occurring extrapyramidal symptoms. Moreover, assuming the appropriate prescribing of antipsychotic medication in the first place infers the presence of significant psy-

chopathology that may also be associated with aggression. As previously mentioned, despite the widespread acceptance that NIA can be associated with aggression, there is surprisingly little documentation of this linkage as only a handful of case reports and studies have been published and any definitive information regarding NIA induced aggression must await appropriately controlled studies specifically designed to answer this question. For as long as data from systematic studies are unavailable, incorporating NIA into a psychiatric-legal opinion would most likely remain but one component in the defendant's relevant state, trait, and ecological factors shaping the defendant's mental state at the time of an alleged crime.

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