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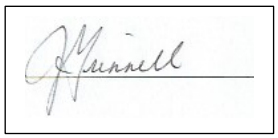
Signature 

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Abstract

This report provides a case of a patient with antisocial personality disorder and major depression within the context of a long-term forensic psychiatry facility who is pursuing off-label use of dextromethorphan-quinidine (Nuedexta) to manage his symptoms of disinhibition, impulsivity, mood lability, and aggression. The patient's symptom severity and risk of harm to self and others; and suboptimal treatment responses to a range of medications necessitated a review of novel treatment approaches. A literature review of dextromethorphan-quinidine in major depression and symptoms of disinhibition, impulsivity, mood lability, and aggression across other psychiatric disorders provided limited high-quality evidence for use within this context due to lack of studies. It remains a novel treatment approach and continues to be regarded as having potential to treat a broad range of psychiatric disorders, and further research is recommended. Despite lack of evidence, dextromethorphan-quinidine may be an appropriate last resort treatment option in those in cases involving major depression or other psychiatric disorders associated with disinhibition, impulsivity, mood lability, and aggression where life-threatening risk of suboptimal treatment exists.

Background

The purpose of this report is to summarize the current evidence of dextromethorphan-quinidine (Nuedexta) in relation to the treatment of a patient with antisocial personality disorder and major depression exhibiting symptoms of disinhibition, impulsivity, mood lability, and aggression. Multiple medication failures as noted within the case report, and lack of FDA approved medications for personality disorders necessitates exploration of novel treatment approaches to target symptomatology. Dextromethorphan-quinidine has been regarded as a novel pharmacological option in the treatment of major depression and many have hypothesized its use across other psychiatric disorders.

The case report involves a patient with antisocial personality disorder and major depression exhibiting primary symptoms of disinhibition, impulsivity, mood lability, and aggression; and unmanaged depression in the context of a long-term forensic psychiatry placement. The patient is being considered for off-label treatment with Nuedexta as a way to manage disinhibition, aggression, and depression symptoms. The complex case history will be provided followed by a review of literature relating to the case. Implications for the patient case and future research and practice recommendations will be provided.

Case Report

A 58-year-old male patient presented with ongoing intermittent disinhibition, impulsivity, mood lability, and aggression in the context of a long-term forensic psychiatry facility in which he resided for over 20 years. His fluctuating disinhibition resulted in multiple instances of verbal

and physical aggression, and suicidal ideation with plan and intent stemming from suicidal and homicidal ideation with concurrent impulsivity.

History of present psychiatric illness

During the course of his stay, the patient demonstrated a longstanding history of suicidal and homicidal ideation, and verbal and physical aggression with fluctuating incidents of severity. Physical assaults directed toward other patients and verbal threats toward staff occurred prior to the encounter. He reported unmanaged depressive symptoms starting decades prior and voiced suicidal ideation during the encounter. He exhibited prominent features of antisocial personality disorder throughout the course of his stay.

Psychiatric History

Psychiatric care began between the ages of 6 and 8 years for behavioral problems and special education services occurred until age 15. The majority of his psychiatric care occurred in the context of a long-term forensic psychiatry placement. Interview and records revealed a history of self-injurious behavior, completed homicide, suicide attempts, and verbal and physical aggression with subsequent legal involvement. Medication trials included: thioridazine, clozapine, olanzapine, risperidone, aripiprazole, quetiapine, lithium, lamotrigine, carbamazepine, buspirone, lorazepam, clonazepam, hydroxyzine, paroxetine, fluvoxamine, fluoxetine, citalopram, trazodone, duloxetine, bupropion, mirtazapine, desipramine, zoplicone, melatonin, propranolol, atenolol, clonidine, gabapentin, topiramate, meclizine, and vitamin d-3.

Pertinent Medical and Social History

Notable components of the social history included terroristic activity which lead to correctional setting placement, and homicide in a correctional setting for which his forensic psychiatry placement was sought. Prior diagnostic testing included The Hare Psychopathy

Checklist-Revised (PCL-R) score of 30. He completed multiple IQ tests throughout his stay and scores ranged from low 90's to 109. The Autism Spectrum Disorder (ASD) Questionnaire screened positive and will be explained later. There were no pertinent co-occurring medical diagnoses.

Diagnostic Formulation

He received a multitude of diagnoses over the years with the most recent diagnoses as Antisocial Personality Disorder; and Major Depressive Disorder, Recurrent, Severe, Without Psychotic Features. Previous diagnoses ranged from Schizoaffective Disorder; Schizophrenia, Paranoid Type; Bipolar 1; to Autism. The patient adamantly denied a history of psychotic symptoms and related the previous report to a meticulous plan to commit violence on the basis of psychotic symptoms in order to secure an alternative placement to prison. The previously mentioned ASD scale largely contributed to a late diagnosis of ASD, however, conduct disorder in childhood with progression to antisocial personality disorder in adulthood better explained the symptoms of inadequate emotional reciprocity and lack of empathy than autism. The patient experienced a major depressive episode approximately 12 years ago and noted feelings of depression, suicidal ideation with plan and intent, hopelessness, anhedonia, and sleep impairment prior to this encounter.

Treatment Plan

The primary goal of treatment included violence reduction by improving disinhibition. Improvement in symptoms of depression was also discussed. He trialed a variety of pharmacological interventions as noted above. Nonpharmacological interventions included individual sessions with a psychologist and behavioral analyst. He also used a weighted vest during times of increased symptoms. Dextromethorphan-quinidine was discussed with the

patient as a novel treatment approach but had not yet been tried due to gaining non-formulary, off-label approval of use.

Literature Review

Dextromethorphan-quinidine (Nuedexta) is a combination drug of dextromethorphan hydrobromide, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and sigma-1 agonist; and quinidine sulfate, a CYP450 2D6 inhibitor (FDA, 2010). It is marketed by Avanir Pharmaceuticals and FDA approved for the treatment of pseudobulbar affect, which is also known as unstable affect or controllable laughing or crying (FDA, 2010; Stahl, 2017). Dextromethorphan works by decreasing the neurotransmission of glutamate by NMDA receptor antagonism and sigma 1 receptor agonism; and potential modulation of serotonin levels due to serotonin transporter affinity (Stahl, 2017). Quinidine works by CYP2D6 inhibition thus increasing the bioavailability of dextromethorphan (Stahl, 2017; Taylor, Traynelis, Siffert, Pope, & Matsumoto, 2016). Notable side effects of this drug include: “dizziness, asthenia, diarrhea, vomiting, cough, peripheral edema, urinary tract infection, *and* euphoria” (Stahl, 2017, p. 207). Immune-mediated thrombocytopenia, hepatotoxicity, and QT prolongation (dose dependent) comprise dangerous side effects (Stahl, 2017).

This review summarizes the evidence of dextromethorphan-quinidine (Nuedexta) for treatment of major depression and other psychiatric disorders involving symptoms of disinhibition, impulsivity, and aggression in relation to the presented case. As noted in the case report, the patient exhibited symptoms of disinhibition, impulsivity, mood lability, and aggression which could be attributed to either his antisocial personality disorder or major depression (Stahl, 2016).

Methods

PubMed and CINAHL Complete were utilized for the review and included articles between 2013 and 2018. The following search terms were used in order to review any relevant indications as the searches yielded a smaller number of articles: dextromethorphan-quinidine, Nuedexta, and dextromethorphan. Reference list reviews were completed with subsequent review of any relevant articles, which added 2 overall articles to the search.

Articles addressing disinhibition, impulsivity, mood lability, and aggression in either major depression or antisocial personality disorder were included. Articles addressing the aforementioned symptomatology in the context of broad-ranged psychiatric disorders were also included due to the newer concept of this treatment approach, complex symptomatology and history of presenting case, and lack of FDA approved treatment options for personality disorders (Perese, 2012). During the search, studies examining dextromethorphan alone were excluded as the quinidine component of the dextromethorphan-quinidine combination increases the bioavailability of the dextromethorphan component which is determined to cause the therapeutic effect (Taylor et al., 2016).

PubMed revealed 238 articles for dextromethorphan-quinidine, with 9 being relevant; 40 articles for Nuedexta, with 4 being relevant; and 482 articles for dextromethorphan, with 2 being relevant. CINAHL Complete revealed 53 articles for dextromethorphan-quinidine, with 3 being relevant; 13 articles for Nuedexta, with 0 relevant; 175 articles for dextromethorphan, with 3 being relevant to the case. After accounting for duplicates and review of reference lists, 15 articles were included in the review.

Results

Overall, the search revealed limited evidence for use and further research was consistently recommended across articles. With regard to dextromethorphan-quinidine and

major depression, lower level evidence of expert opinions, literature reviews, and one case report supported its use. One open-label, proof-of-concept trial, which was not funded by conflicting interests, demonstrated some higher-level evidence and was based off of a sample size of 20 with thorough explanation of limitations including patients treated both with and without concurrent antidepressants, lack of control group, small sample size, and lack of blood samples to detect therapeutic samples; although appropriate doses were administered based on pharmacokinetic evidence (Murrough et al., 2017).

With regard to dextromethorphan-quinidine and disinhibition, impulsivity, mood lability, and aggression, the search revealed some low-level evidence such as expert opinions and case reports to support its use within a variety of psychiatric disorders, none of which being antisocial personality disorder specifically. Within the literature review, some of the authors disclosed conflicts of interest due to being paid by Avanir Pharmaceuticals as noted below. One randomized controlled trial of a small sample size demonstrated effectiveness in the agitation/aggression component of Alzheimer's. One clinical practice guideline on bipolar disorder indicated that no recommendations could be made in bipolar II due to limited evidence but recommended further research.

Nuedexta and major depression. The search revealed limited evidence on the use of dextromethorphan-quinidine in Major Depression, but it is well documented as a novel treatment consideration for treatment resistant depression (Henter et al., 2017; Jaso et al., 2017; Lapidus, 2013; Larate, Kadriu, & Zarate, 2017; Lonescu & Papakostas, 2017).

Garay et al. (2017) searched for current drugs being investigated in treatment resistant depression and found one trial examining dextromethorphan-quinidine completed by Murrough et al. (2017). Murrough et al. (2017) published the results of their phase IIa open label clinical

trial, sponsored by Murrough, on the use of dextromethorphan-quinidine in 20 adult patients with treatment resistant depression related to effectiveness and tolerability. Murrough et al. (2017) determined tolerability in this population as well as preliminary efficacy at doses up to 45/10 mg every 12 hours. Messias and Everetts' (2012) case report described the off-label use of dextromethorphan-quinidine in a patient with emotional lability associated with depression. At the time that their article was published, the patient demonstrated an improvement in affective expressions for greater than one year (Messias & Everett, 2012). The most reliable article relating to depression indication included the proof of concept trial completed by Murrough et al. (2012) but larger randomized controlled trials are needed as the sample size was 20. Various expert opinions hypothesized its potential use and recommended continued research. The case report also demonstrated efficacy and tolerability but did not produce high level evidence (Messias & Everett, 2012).

Nuedexta and antisocial personality disorder, disinhibition, impulsivity, mood lability, and aggression. In the novel concepts of neuroscience, Stahl (2016) indicated that the impacted brain circuits of PBA may be similar to the brain circuits in other psychiatric disorders involving dysregulation of emotions; and that dextromethorphan-quinidine could potentially address these symptoms across these psychiatric disorders.

Research has been completed on dextromethorphan-quinidine on emotional volatility in TBI and bipolar II and bipolar NOS with some documented tolerability and efficacy (Garcia-Baran, Johnson, Wagner, Shen, & Geers, 2016; Kelly & Lieberman, 2014). Taylor et al. (2016) reviewed the pharmacology of dextromethorphan-quinidine and included future targets of treatment but the search did not reveal any completed studies to date. Taylor et al. (2016) also

disclosed that their study was funded by Avanir Pharmaceuticals and two of the authors were paid consultants to Avanir Pharmaceuticals.

As mentioned in the above section relating dextromethorphan-quinidine and depression, Messias and Everett (2012) published a case report which reported the effectiveness of dextromethorphan-quinidine in emotional lability associated with depression; and hypothesized the possibility that the alterations in affective expression are similar in both pseudobulbar affect and mood disorders. Mathys (2018) reviewed the pharmacological management of behavioral and psychological symptoms associated with neurocognitive disorders and listed dextromethorphan-quinidine under agents supported by limited evidence due to having only one randomized, placebo-controlled trial of agitation in Alzheimer's disease (Cummings et al., 2015). The randomized controlled trial completed by Cummings et al. (2015) demonstrated significance to the case in that it measured severe agitation and aggression in the use of dextromethorphan-quinidine. In the 2018 Guidelines for the management of patients with bipolar disorder, Yatham et al. (2018) included dextromethorphan-quinidine as an agent with no specific recommendation and requiring further study based off of the limited evidence.

Implications

Based on this literature review, it is apparent that potential benefits are possible with the use of dextromethorphan-quinidine for a range of psychiatric disorders involving disordered emotional expression, however, the current evidence suggests that this is still a novel treatment approach lacking the required level and amount of evidence to support its safe and effective use. Large, high quality studies on the safety and efficacy of dextromethorphan-quinidine across related psychiatric disorders are recommended. It is also important to note that studies including dextromethorphan alone are not sufficient as the quinidine component increases the availability

of dextromethorphan, so previous studies could theoretically be based off suboptimal doses (Taylor et al., 2016). Providers considering the use of dextromethorphan-quinidine for behavioral disinhibition and mood lability across various psychiatric disorders should thoroughly review the most current evidence and patients' prior treatment failures as the current evidence does not indicate it as first line use for major-depression or behavioral disinhibition in antisocial personality disorder. Depending on symptom severity of major depression and/or behavioral disinhibition in antisocial personality disorder, dextromethorphan-quinidine may be an appropriate option in patients with multiple treatment failures.

As for the patient in the case report, he demonstrated a multitude of medication trials in order to manage his symptoms of disinhibition, impulsivity, mood lability, and aggression and reported suboptimal treatment of his depressive symptoms. He remained in a secure forensic-psychiatry facility without treatment progression and continued to engage in physical aggression putting himself and others at risk of harm. His medical history did not reveal an increased risk for serious side effects to dextromethorphan-quinidine. Considering his treatment resistant depression with aforementioned medication trials, impulsivity and aggression with risk of harm to self and others, and stagnant treatment progression; dextromethorphan-quinidine may be an appropriate medication trial if genetic testing reveals that he is an appropriate CYP2D6 metabolizer. The potential benefits of possible reduction in depression symptoms, disinhibition, impulsivity, mood lability, and aggression with subsequent treatment progression; and streamlined medication regimen seem to outweigh the known risks, or lack thereof, at this time. Psychoeducation regarding its off-label use is paramount.

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