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Case Study: Assessment and Management of Medication (DULOXETINE) Induced Abnormal Involuntary Movement.
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A Retrospective Comparative Chart review of prescription patterns of Trazadone and Zolpidem in an Psychiatric outpatient clinic shows equal patient preference and benefit profile

Omar Shah, MD, Syed Jamal Mustafa, MD, Atif Akhter, MD, Khaled Ahmed, MD

ABSTRACT:

Two commonly prescribed medications to address sleep problems, in psychiatric outpatient setting Trazadone and Zolpidem (AMBIEN) were compared in a chart review, and assessed for efficacy and patient preference. This article focused on patient preference for either medication as evidenced by either a direct patient request for that medications, and once initiated the duration of treatment time before a change in medication was requested, or the total duration of treatment for medication. The authors reviewed 101 charts, in which sleep was identified as a clinical concern and was treated with a medication option. Sleep Hygiene was routinely discussed with patients, however the charts did not track compliance with proper sleep hygiene techniques by the patients. The efficacy of the medication was noted by the time duration from when the improvement in the symptoms (sleep) had been established and maintained to the point that the patient no longer needed or desired to continue medications. The findings indicated that both medications were efficacious, and by day 270, only 7% of the patients in either cohort, continued to need to use the medications. The self-reported satisfaction and improvement was also equal with both groups. As the two medications were noted to be almost equal in preference and efficacy, then reviewing the Cost Benefit Analysis indicated that it might be beneficial to try Trazodone for sleep issues before trying a more costly option such as zolpidem (AMBIEN).

INTRODUCTION

Insomnia is a common medical complaint. It is a term which refers to difficulty initiating sleep, difficulty maintaining sleep and early morning awakening and inability to fall sleep again (American Psychiatric Association, DSM-5, 2014) It is the most prevalent sleep disorder, occurring in 19% to 50% of clinical patients seeking treatment in the outpatient setting (Katz DA, 2002), (National Sleep Foundation., 1995), (Culpepper, 2006). One of the main features of insomnia is difficulty initiating sleep, defined as subjective sleep latency of more than 20 to 30 minutes (Katz DA, 2002). A study noted the prevalence of insomnia was as high as 69% in primary care patients (Shochat T, 1999). Also, a recent national survey of non-institutionalized adults reported a 35% insomnia prevalence rate during the course of the year, with insomnia affecting women more than 50% of the time (Mellinger GD, 1985). About 20% to 36% of patients are affected by insomnia chronically which lasts for a duration of greater than 1 year (Bixler EO, 1979), (Chevalier H, 1999), (Hohagen F & 242(6):329–336., 1993), (Vollrath M, 1989; 239(2):113–124.), (Zeitlhofer J, 1994;). Insomnia is a symptoms of many psychiatric illnesses and can also present as a co-morbidity with other psychiatric illness with a large number of patients presenting with insomnia (Becker, 2006). Although common, the importance and incidence of insomnia is often underestimated, especially in the elderly. This can be an issue as it is associated with a significant increase in morbidity and mortality in the elderly. Nursing home visits are greatly increased due to sequelae of insomnia (Ancoli-Israel, 2000; 23 (Suppl 1):S23–30 (discussion S6–8)).

In addition to its prevalent, insomnia is associated with various sequelae and quality of life issues. Moreover, not all medications are universally available, affordable or effective. Medications especially proprietary name-brand medications, can at times be cost prohibitive, the authors decided to perform a chart review to see if there is any cost justifiable benefit to one medication over the other.

The results were not surprisingly different from anecdotal observations, but the results are a good informative discussion point that can be shared with patients, in aiding them make informed decisions about the medications that they may wish to choose for their insomnia.

To study the effectiveness of medications used
to treat insomnia, and to note the preferences of the patients, the authors identified TRAZODONE and AMBIEN as the two medications to compare. This was also based on the preponderance of the prescription written for these two medications in the out-patient clinic.

METHOD:

A total of 101 charts from outpatient clinic were reviewed. Those charts were included in the review, which listed Insomnia as an identified concern and either TRAZODONE or AMBIEN were prescribed for Insomnia issues.

The factors that were studied, included the total duration of time that the medication was used in days, and frequency of prescription of each medication and rates of discontinuation.

Duration on trazodone and/or zolpidem was calculated in days from first day of treatment till the last day of treatment or up to the arbitrary date 365 days from start of treatment.

Subjective improvement in sleep (Quality and Duration as well as general Satisfaction by the patient) were inferred from chart records during the follow-up visits.

Of the 101 charts reviewed, 63% were of female and 37% were male patients. Amongst the male patients, 71% had prescriptions for AMBIEN and 29% had prescriptions for TRAZODONE. In contrast 69% of female patients were on TRAZODONE and 31% were on AMBIEN.

It was also noted that of all total prescriptions written for insomnia in both male and female patients, TRAZODONE was prescribed almost twice as often than AMBIEN. Patients who took either TRAZODONE or AMBIEN both reportedly continued with medications, noticing improvement with adequate tolerability to their respective medications. In both group of patient it was noted that by Day 270 from the date of the initial prescription less than 7% of the patients (Male or Female) were still using any medication (AMBIEN or TRAZODONE), this ratio remained fairly constant till the end of the observation period of 365 days.

When the discontinuation data of the two medications was compared, it was noted that in the first thirty days of commencement of treatment there were no drop outs from the group taking AMBIEN, whereas almost 14% of patient who started TRAZODONE had stopped taking their medication. Although the exact reason that TRAZODONE was discontinued was not captured in the charts, it appears that the assumption was that the medication was no longer needed to address insomnia. However of those subjects who continued to take their medications, within 90 days, the discontinuation rates of both medications (TRAZODONE and AMBIEN) were almost similar.

No Adverse Events or Side Effects were noted in the charts, therefore the reason for termination of treatment with medications at various time points was assumed to be resolution of the initial insomnia.

DISCUSSION

Many pharmacological agents are used to treat insomnia, some of these medications are used “Off Label”.

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Zolpidem, a non-benzodiazepine compound is one of the most common medications for treatment of insomnia. Zolpidem has been shown to cause minimal risk of withdrawal or abuse. It can be used for symptoms of initiation of sleep and middle of the night awakening. However, the drawbacks include rebound insomnia, next-day residual effects (after middle-of-the-night dosing) and complex sleep-related behaviors such as on ability to drive, memory, and psychomotor performance (Lichtenwalner M, 1997). Various studies support the efficacy, safety and tolerability of zolpidem, in adults including the elderly (Katz DA, 2002), (National Sleep Foundation., 1995), (Culpepper, 2006), (Mellinger GD, 1985), (Zeithofer J, 1994;). There is minimal risk of abuse or dependence with administration of zolpidem in this population (Aragona, 2000), (Morinan A, 2010), (Sadock BJ, 2007;), (Perrault G, 1992), (Liappas IA, 2003;)

Trazodone is a serotonin antagonist and reuptake inhibitor (SARI) that has been used for the treatment of MDD with or without anxiety since as early as the 1970s (Feighner JP, 1988). At lower doses than those used for the treatment of depression, trazodone is thought to be act primarily by antagonizing 5-HT2A receptors. H1 receptors and a1-adrenergic receptors (Stahl, 2009).Trazodone has efficacy similar to other second generation anti-depression medications. Trazodone is not FDA approved for insomnia or sleep disorders, however it is used as part of standard practice in many outpatient settings (Stahl, 2009), (Brogden RN, 1981). It is tolerated well and has fewer anticholinergic effects than TCAs (Tri cyclic antidepressants) such as imipramine and amitriptyline.

BENZODIAZEPINE group of medications are effective as hypnotic agents, however they do have certain drawbacks, including their propensity to be habit forming. They can also lead to dependency and even abuse if not monitored and used judiciously. In addition, Benzodiazepines can also cause central nervous system side effects like ataxia, anterograde amnesia, falls leading to potential complications such as motor vehicle accidents.

ANTI-HISTAMINES are effective Hypnotic agents, histamine blockade causes sedation. However, Anti-Histamines can cause central and peripheral anticholinergic side effects, and the sedative/hypnotic effects are relatively short-lived. Furthermore, in younger patients, Anti-Histamines can lead to paradoxical symptoms which may negatively effect insomnia treatment. In the chart review it was noted that of the two medications (AMBIEN and TRAZODONE), TRAZODONE was prescribed twice as much as AMBIEN for females. However irrespective of which medication was used initially for treatment of insomnia, by DAY 270, less than 7% of people needed to continue either medication for insomnia, reporting a resolution to their sleep problems.

The authors did note that both groups of patients tolerated the medications without any discontinuations because of Adverse Effects.

The authors also pondered over the reason why trazodone was prescribed more than Ambien, and more for female patients. Prescriber preference for one medication over another, usually is an indication of that medications past positive performance in similar patients. Another reason is usually patient request for a specific medication. Trazodone being in the family of Anti-Depressants, it was also considered that some patients may have been preferentially prescribed TRAZODONE to address sub-clinical manifestation of anxiety of depression.

The authors acknowledge that there may have been many reasons for the prescriptions of trazodone outnumbering the prescriptions of zolpidem in the psychiatric outpatient setting for patients, regardless of patient psychiatric diagnosis. However the true reason for such a discrepancy was not noted in the charts, therefore the reason can only be speculated and is beyond the scope of discussion of this article.

Trazodone is commonly used as a sleep aid and an anti-depressant medication (Stahl, 2009), (Brogden RN, 1981). Psychiatrists use trazodone for both indications (Scharf MB, 1990;), (Thase, 1999), (Evans SM, 1990; 255:1246– 1255.). Also, in psychiatric patients, both conditions coexist in many individuals (Passarella S, 2008), (Weyerer S, 1991), (Scharf MB, 1990;), (Thase, 1999), (Evans SM, 1990; 255:1246– 1255.) making trazodone an attractive option.

Another reason for Trazodone being prescribed more than Ambien, could be that patients choose to take trazodone over zolpidem because of its dual nature as a sleep aid and antidepressant (Stahl, 2009), (Brogden RN, 1981), thus making it seem more reasonable to take than to add another sleep medication.
Thirstily, AMBIEN is considered by many to have habit forming potential (Rush CR B. R., Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans., 1999), (Caroline Victorri-Vigneau PhD, (2014)), which could have contributed to a hesitancy by the prescriber to initiate insomnia therapy with AMBIEN, or the patient/patient’s family asking for an alternative medication. Trazodone does not seem to have the habit forming properties that Zolpidem does. This may well have played a noticeable role in patients either choosing or physicians prescribing trazodone over zolpidem.

Another consideration is the Cost Benefit Analysis perspective. TRAZODONE is a more affordable option than ZOLPIDEM. According to Epocrates, generic TRAZODONE 50 mg Tablet costs $34.84 for 60 tablets and the cost for 100mg Tablet is $48.75 for 60 tablets; whereas name brand AMBIEN 10 mg costs $241.99 for 30 tablets and AMBIEN CR 12.5 mg is $287.99 for 30 tablets.

CONCLUSION:

Both zolpidem and trazodone are commonly prescribed medications for insomnia and have never been compared in such a manner in an outpatient clinical setting. Through chart review and analysis of the data, it is evident that both AMBIEN and TRAZODONE are effective medications. Overall both medications were well tolerated, and their duration of use and discontinuation patterns were also very similar. However the cost differential is between the two medications is considerable.

Currently TRAZODONE appears to be a more cost effective first line option for insomnia. It is also equally important to emphasize the importance of behavior modification and implementation of good sleep hygiene.

The authors acknowledge that this report is by no means exhaustive in its learning objectives, the one fact that has become clear is that further investigation is warranted. Further studies would be beneficial to probe the reasons why some patient prefer one medication over another.

There are various levels of practitioners (Specialist Physicians, General Practice Physicians, as well as med-level practitioners) who prescribe medications used for insomnia. On numerous occasions, patients request that their physicians prescribe a certain medication to them. As responsible physicians it is our duty to provide our patients with the best information available about the medications, their efficacy as well as their comparative benefits; which should also include a Cost Benefit Analysis.

Trazodone showed similar results to zolpidem for treatment for insomnia. At the end of the day, it is cheaper and is more commonly used than zolpidem, an accepted FDA approved medication for insomnia. More evidence for its efficacy may help patients and physicians alike, to feel more comfortable to use it as treatment for insomnia.

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INTRODUCTION:

Opioid misuse in the United States has been a problem, which recently appears to have become even a more significant problem. In 2010, an estimated 200,000 persons reported heroin use, 5.1 million individuals age 12 years and older reported non-medical use of prescription pain relievers in the past month (American Psychiatric Association, 2014). The number of individuals with Opioid dependence increased from 1.5 million in 2002 to 1.9 million in 2010 (American Psychiatric Association, DSM-5, 2014).

Opioid dependence is a cluster of physiological, behavioral, and cognitive symptoms, which together indicates repeated and continuing use of opioid drugs, despite significant problems related to such use.

Addiction is often characterized by periods of abstinence, followed by a relapse episode (O’Brien CP, 1998). The most important objective for clinicians is prolonging the time to relapse, and not necessarily preventing relapse (J., 2000).

Many previous studies has shown that relapse can increase due to a number of factors, including stress (TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction; SMA07-3939, 09/2004), environmental stimuli that signal the availability of the drug (Mattoo SK, 2009), and a high number of undesirable life events, physical changes in brain structure and modified neurotransmitter levels due to drug use, also affect the probability of relapse (O’Brien CP, 1998).

Traditionally, federally regulated programs such as methadone clinics have been at the forefront of treating opioid dependence patients. Fortunately since the past decade, The Drug Abuse Treatment Act of 2000 enabled US physicians with additional training to prescribe Buprenorphine/Naloxone (SUBOXONE) for Opioid Dependence Treatment in outpatient clinical setting (Wesson, (2010). Several factors favor use of SUBOXONE in outpatient clinics including convenient access, customizing dose to the needs of patients and integrated treatment of the psychiatric comorbidities (Feillin D, 2002).

A commonly accepted theory of the “reward pathway” in brain is said to be in the mesolimbic dopamine system. The circuit is activated by natural rewards, such as food, sex, social interactions. These same pathways can also be activated by substances such as Opiates. This pathway is therefore an important determinant of incentives and may motivate an individual to repeat

SUBOXONE (Buprenorphine/Naloxone) Treatment alone is not enough to prevent relapse in Opioid dependence with comorbid Psychiatric illness.

Narayan Chaudhary, MD, Syed Jamal Mustafa, MD, Wisam Aljumaili, MD, Syed Kamal Mustafa, MD, Khalid Ahmad, MD, Sadaf Amir, MD, Omar Shah, MD

ABSTRACT:

Opiate Dependence is a condition of epidemic proportions with serious Bio-Psycho-Social and Socio-Economic ramifications. Traditionally most Chemically Dependency Treatments in past have been seen through a unidimensional lens, with blame being put firmly on the shoulders of the individual afflicted with the burden of Chemical Dependency issues. Fortunately this attitude continues to change and more treatment algorithms are recognizing and implementing a systemic multi-disciplinary approach to treating Chemical Dependency Patients. As this approach is gaining acceptance and momentum, treatment teams are more open to adopting this approach, and now a potential limitation might be in getting the patients and families on board with the approach of treating Opiate Dependence as well as the co-occurring psychiatric co-morbidities. It is often in a Psychiatric treatment setting, when patients are evaluated for Opiate Dependence and they are also found to have psychiatric comorbidity. Our study gave strength to the hypothesis that if we aggressively treat co-occurring psychiatric co-morbidities along with Opiate Dependence, patients responded positively by fewer relapses, and a prolongation in the time to relapse.
destructive patterns of behaviors (American Psychiatric Association, DSM-5, 2014). Buprenorphine preferentially binds with strong affinity to the mu opioid receptor in the brain, preventing other opiates from binding to the receptor and consequently inhibiting the euphoric pleasurable effects of opioids (Feillin D, 2002). The clinic based availability of buprenorphine/naloxone (SUBOXONE) as a treatment option has significantly enhanced the accessibility to treatment for many patients, with consequent improvement in the quality of life as well (Fudala PJ, 2003).

Despite the fact that SUBOXONE treatment allows more convenient, flexible and individually tailored treatment for patients with Opiate Dependence, the numbers for incidence of relapse have not significantly changed in the past 10 years. It was hypothesized by the authors that unless co-morbid psychiatric issues are also addressed in SUBOXONE treatment protocols, the time to relapse and relapse rates will not be significantly changed with SUBOXONE alone.

METHOD:

Charts were reviewed in an outpatient psychiatric clinic setting where patients who met criteria for Opiate Dependence were treated using the PSPC SUBOXONE Treatment Protocol (PSTP). For the purposes of this study, relapse was defined as the use of non-prescribed opiates (as confirmed by 10 panel Drug Test) during the course of treatment, (with or without drop-out from the treatment protocol).

This study, retrospectively examined Relapse Rates (RR) and the Time To Relapse (TTR) for the patients once they started Out-Patient SUBOXONE Treatment using the PSTP.

PSPC SUBOXONE Treatment Protocol, (Syed Jamal Mustafa, 2014), is a structured treatment protocol followed at the Puget Sound Psychiatric Center. It starts with screening patients for Opiate Dependence to be treated in an outpatient setting, where patients are provided with symptoms relief with a “rescue medication cocktail” which includes SERQUEL, NEURONTIN, CLONIDINE and BACLOFEN. After induction is complete the patients go into the maintenance phase of monthly SUBOXONE monitoring and medication checks, as well as preferably weekly, but at least twice a month psychotherapy; and regular support groups (AA/NA). It is during this time that the patient is in active treatment of any co-morbid psychiatric disorders as well.

It has been the claim of the Puget Sound Psychiatric Center, that treatment of Opiate Dependence is better when conducted as per PSTP, (addressing both Opiate Dependence and Co-Morbid Psychiatric Disorders) this claim was tested by the chart review process and comparing to currently available national epidemiological figures.

Data was collected from 60 charts selected for a retrospective review. Data collected included patient demographics, diagnosis, substance use history, date of intake and relapse, relapse substances, reason of dropout or discharge. Treatment team included Buprenorphine certified psychiatrists, neurologist, Psychiatry Residents, Chemical dependency Certified Therapist. At intake, detailed history had been obtained, (including psychiatric, substance abuse, medical, and psychosocial histories). Urine Drug Screen (UDS) and clinically relevant routine labs had been ordered.

Patients who met criteria for Opiate Dependence were enrolled in the PSPC Suboxone Treatment Protocol (PSTP).

During the intake process it was noted that 88% of these patients also met criteria for one or more Psychiatric Co-Morbidities.

During the PSTP, Stabilization and Maintenance phases, psychiatric comorbidities were also addressed along with Opiate Dependence, and treatment was tailored within the PSTP format to suit the clinical needs of the patient.

At visits to the clinic Drug Screens are routinely obtained as part of the PSTP. Relapse was determined by positive drug test or patient self-report during the period of treatment. The primary outcome, time to relapse was calculated from the start date of buprenorphine till the date of positive opiate result at the clinic visit. Secondary outcomes measures such as Relapse Rate and associations between relapse and comorbid psychiatric disorder were separately calculated.

RESULT:

A total of 60 patients chart were reviewed. The age range of subjects reviewed was between 18-65 years. There were 32 males and 28 females
All patients had Opiate Dependence, 88.33% of these patients also had co-morbid psychiatric diagnosis, and 10% of these patients relapsed. It was noted that during the review period of almost 36 months, the mean Time To Relapse (TTR) was 22 months from the start of Buprenorphine treatment (the range of TTR was from the 15th month mark to the 34th month mark), the Median TTR was noted to be 20th month; whereas the Mode TTR was the 15th Month.

Amongst those patients who relapsed 33.33% had no psychiatric co-morbidities. Whereas of the patients who did not relapse 90.73% had Psychiatric Co-Morbidities, The psychiatric co-morbidities included ADHD, Anxiety Disorder, Depressive Disorders and Mood Disorders (including possible Bipolar Disorders).

These results indicate that those patient who were being treated with the PSTP, with or without Psychiatric co-morbid conditions had a better prognosis, and a lower relapse rate (RR) and longer Time To Relapse (TTR). Smyth BP, et al report that up to 90% of all people with Opiate Dependence relapse.

The study also revealed that for those patients without co-morbid psychiatric illness the RR (Relapse Rate) was almost three times higher than for patients without psychiatric co-morbidities.

DISCUSSION:

Opiate Dependence is a complex topic, the full magnitude of which is not completely understood at this time. It is commonly accepted that SUBOXONE is used to treat Opiate Dependence, however the definition of treatment for Opiate Dependence is the point of contention for many. Some purist may say that Opiate Dependence Treatment must mean being clean and free from the offending agent (Opiates in this case) and also there should be no relapse. Many professional use the analogy of Diabetes Mellitus, and compare Opiate Dependence to such Chronic Illnesses. Irrespective of who is right or wrong, the bottom line is that Opiate Dependence has vast implications in Human Society, on the one hand Opiates help ease painful conditions, on the other hand its Addictive Qualities make Opiates debilitating for those individuals who succumb to the “Addiction”, then of course comes the stigma of being an “addict”. Many individuals who are dependent on Opiates have Psychiatric Co-Morbidities, and if the patients have Psychiatric Co-Morbidities, it is important to identify them early and treat them accordingly. If a co-morbidity is treated appropriately then Opiate Dependence Treatment with SUBOXONE can be very promising and can almost reach the goals of total abstinence.

Our findings show that when psychiatric co-morbidities are appropriately treated, the TTR (time to relapse) and RR (relapse rate) both change favorable. Furthermore with continued and ongoing treatment of the co-morbid psychiatric conditions, relapse can be something to completely overcome.

CONCLUSION:

The high prevalence of psychiatric comorbidities highlights the need to adhere to a structured broad based treatment program such as the “Puget Sound Psychiatric Center SUBOXONE Treatment Protocol” (PSTP) which in our study has shown to be extremely successful in pre-
venting relapse at a rate phenomenally under the national averages.

The focus of the PSTP, is not just the Opiate Dependence, but that Psychiatric Co-Morbidities should be treated aggressively and consequently Opiate Dependency can be brought under much success.

This approach is in line with the understanding of Ferri M. et al (M., January 2014) that comorbid psychiatric or substance abuse conditions, psychosocial stability, and a patient’s adherence history with other medications may all influence compliance with buprenorphine and prevent relapse. O’Brien, C.P. et al (O’Brien CP, 1997) suggested that there is association between comorbid depression and higher treatment retention in heroin dependent patients (O’Brien CP, 1997), our findings partly are in agreement, showing that if the patients’ co-morbidity is being adequately treated then they stay in treatment longer with fewer relapses.

Our study has a number of limitations, the most notable one being its small sample size and the duration of treatment for this co-hort. Another limitation is the retrospective chart review study design. These factors limit the ability to control quality of assessment and collection of more detail data. However it does fuel the fire to gain knowledge and prepare for a future follow-up and larger study.

This study confirms that, SUBOXONE is effective treatment in preventing relapses and prolonging relapse time when the psychiatry comorbidity is simultaneously and aggressively treated in specialized outpatient setting.

References


Case Study: Assessment and Management of Medication Induced (DULOXETINE) Abnormal Involuntary Movements:

Sadaf Amir, MD; Syed Jamal Mustafa, MD; Khalid Ahmed, MD, Syed Kamal Mustafa, MD.

ABSTRACT:

The awareness of the occurrence of mental health illness in younger age group has substantially increased in recent years, consequently so have the prescriptions of psychotropic medications at midlevel, primary care and specialty care level. In any given month in most cities in the USA which have an active Pharmaceutical representative community, practitioners are exposed to branded information studies talking about the benefits of second generation atypical psychotropic medications. Also being highlighted is their proposed role in numerous mental health diagnosis, from Schizophrenia, to Depression, to Autism, to various phases of Bipolar Disorder. It is acknowledged that the pharmaceutical agents available today are vastly superior in their effectiveness (both efficacy and tolerability) as compared to their predecessors (first generation/Typical Anti-psychotics), however this piece of information should not cause the Doctors and Practitioners to lower their guard when it comes to judicious and appropriate use of such pharmaceutical agents. Various side-effects are discussed in Package Inserts, as well as print and electronic versions of prescribing aids and tools including, PDR, Epocrates etc. Despite the fact that they are not very common, the risk of movement disorders should be cautiously evaluated before prescribing or augmenting with anti-psychotic medications, and monitoring of abnormal movements needs to be done more frequently. Another very important factor to consider is the fact that due to overwhelming shortage of Trained Psychiatrist, and the phenomenal increase in the mental health needs in children, adolescent and adults (young and old), therefore those non-psychiatric Prescribers who prescribe Psychiatric Medications, including Primary Care, Family Practice and Pediatric Physician, as well as mid-level providers (Nurse Practitioners and Physician Assistants) should be trained more thoroughly with more exposure and supervised training according to current guidelines. The following case brings to light the complexities of assessing and then managing medication induced Abnormal Involuntary Movements.

CASE REVIEW:

This case is of a 24-year-old white male, being treated in an outpatient setting, for paranoid schizophrenia, with additional symptoms of inattention, distractibility and feelings of anxiety and being on edge; who was psychiatrically stable for the past three years on his medication regime of GEODON, ADDERALL and NEURONTIN. Patient also had a past history of alcohol use, which is in early remission at present (American Psychiatric Association, DSM-5, 2014).

The patient presented to the clinic six days after having initially developed jaw pain that evolved over the next two days, into abnormal involuntary movements of the jaw and possibly tongue. The unscheduled appointment, was requested by the patient’s mother who was concerned about the patient being in obvious distress after taking one only dose of DULOXETINE which was prescribed by his Primary Care Physician, to address depression symptoms that he had reported to the PCP during a routine visit.

The patient and mother were also concerned that the abnormal movements had not remitted despite the medication (DULOXETINE) having been discontinued by the patient. The patient reports that during the past six days, he had visited the local hospital Emergency Department once, where a dose of BENADRYL was administered with only brief (2-3 hours) relief from the symptoms.

On examination abnormal involuntary movements manifested by continuous noticeable opening and closing of jaw and possible writhing movement of tongue inside mouth were observed (Bucco-Oro-Masticatory). The movements were causing functional deficits such as difficulty speaking and to some degree swallowing. The patient’s mother reported that the movements diminished while the patient was asleep, and were noticeably exacerbated by physical exercise, anxiety and stress. The movements created emotional disturbances such as fearfulness, low mood, and feelings of hopelessness in the patient.

After a review of history and systems, and examination; a provisional diagnosis of drug-induced dystonic reaction, “Acute Oro-Mandibular Dystonia” was made, other causes of dyskinesia were also considered and systematically excluded (J.Milstein, 2013). The patient and family wanted medication regime to be changed, to provide relief. As no definitive answers were available, the theory of what might have occurred and what medications could potentially be beneficial to the patient was explained in detail to the patient and patient’s mom. After obtaining informed consent treat-
ment was initiated with LORAZEPAM, NEURONTIN, COGENTIN and VITAMIN-E. The patient tolerated the regime. The response to treatment as evidenced by amelioration of symptoms was slow but noticeable. By the end of six months there was no observable abnormal involuntary movement.

DISCUSSION:
In a review of U.S. Food and Drug Administration Adverse Event Reporting System was researched and it was found that 89 patients with antidepressant induced Extra Pyramidal Symptoms had been reported between 2005 and 2008. Fifty-nine of the reported cases were due to duloxetine (Albayrak & Ekinci, 2012), and 6 of them had acute dystonia (J. Milstein, 2013). There have been several case reports of acute dystonia in patients who were treated with antidepressant agents (Stahl S. M., 2014) (Alan F. Schatzberg & Charles DeBattista, 2013) such as fluvoxamine, sertraline, fluoxetine, cilatropram, mirtazapine, paroxetine, venlafaxine and bupropion. (Görkem Karakaş Uğurfu, 2013)

A case of Duloxetine induced tardive dyskinesia was reported in a 62-years old female with Major Depressive Disorder who developed dyskinesia when she was in her fourth month of treatment with duloxetine. The dyskinesia was reported to have remitted with fluvoxamine. (Albayrak & Ekinci, 2012)

Another case of tardive dystonia and tardive dyskinesia was reported in a 58-year-old female with major depressive disorder, who developed distressing oral dyskinesia, mandibular dystonia after treatment with duloxetine (30–60 mg per day) for 18 months. Despite discontinuation of duloxetine, she only had partial remission. (Pei-Yi Chen, 2010)

The authors of another article titled as "extrapyramidal symptoms associated with antidepressants" concluded after review of the literature and analyzing case reports that it is essential to recognize that EPS have been reported with different classes of antidepressants (SSRIs, SNRIs, NDRIs), are not dose related, and can develop with both short-term and long-term use. (Subramoniam, MD Lada, MD Renata, & MD Ronald, 2010)

In the above mentioned cases, the monotherapy suggested that duloxetine was directly associated with dyskinesia. In contrast the patient case report presented in our case was being prescribed polypharmacy, which made associations difficult to determine.

The authors in the case being presented also made an attempt to investigate whether it was a drug interaction or duloxetine itself that was primarily responsible for the dystonia?

In summary; Duloxetine (Cymbalta) increases Serotonin and Nor-epinephrine by presynaptic reuptake inhibition of Norepinephrine and Serotonin. Whereas Ziprasidone (Geodon) increases Dopamine by antago-

nism of Dopamine D2 receptor and Serotonin 5HT2A receptor. (Stahl S. M., 2013). Amphetamine Salts (Adderall) increase Dopamine and Nor-Epinephrine in prefrontal cortex by (i) Presynaptic reuptake inhibition of Norepinephrine and Dopamine and (ii) increasing presynaptic Dopamine release. (Stahl S. M., 2013). Gabapentin (Neurontin) increases GABA by (i) increasing the transport of GABA through Blood Brain Barrier, (ii) increasing GLU-DE (Glutamic Acid Decarboxylase; the enzyme needed for converting Glutamic Acid to GABA) and (iii) inhibiting GABA- T (GABA-Transaminase; the enzyme needed for catabolism of GABA) (Mark A. Frye)

Dystonia (lit, abnormal muscle tone) is a neurological condition characterized by involuntary and sustained muscle spasms that can force affected parts of the body into abnormal movements or postures. Unlike other movement disorders, which result from unopposed contractions of a muscle group (chorea) or alternating contractions of agonist and antagonist muscle groups (tremors); dystonias results from the simultaneous contractions of agonist and antagonist muscle groups. (J. Milstein, 2013)

PATHOPHYSIOLOGY OF ACUTE DYSTONIC RE-ACTIONS: The exact pathophysiology of acute dystonic reactions remains unknown. (Görkem Karakaş Uğurfu, 2013). However there are theories that deserve out attention as to the possible etiology of Dystonias, which aid us in formulating a comprehensive management plan. The various theories could be any one of the following;

Lack of Dopamine. The temporal relationship to dopamine blockade suggests that lack of dopamine activity may cause dystonic reactions. However this theory does not explain why antidepressant like SSRI and SNRI cause dystonic reaction.

Dopamine Blockade induced Positive Feedback Loop. In response to drug-induced dopamine blockade, a feedback loop may provoke an imbalance in secretion of dopamine or a dopamine-like neurotransmitter that may lead to dystonic movements.

Excessive Cholinergic Activity. Favorable responses to anti-cholinergic medications suggest that excessive cholinergic activity may have a role to play in dystonic movements.

The exact mechanism of causation of duloxetine and other antidepressant-associated dystonia is unknown (Subramoniam, MD Lada, MD Renata, & MD Ronald, 2010). Plausible mechanisms may include inhibitory modulation of dopaminergic functions in the nigrostriatal pathways: the reciprocal balance between dopaminergic, serotonergic, noradrenergic, or cholinergic activity.

MANAGEMENT APPROACH
Irrespective of what might be the causative factor in Dystonia, the uphill and daunting task of the physician
remains to provide management i.e. comfort, support and treatment.

Management of Dystonia is a multi-step process, unfortunately with no guarantees.

**STEP ONE: RISK FACTOR ASSESSMENT:**
The risk factors for dystonic reactions include younger population, male gender, comorbid psychiatric illnesses, co-morbid substance abuse, previous ECT, and pre-existing brain damage. In particular, individuals who have abused cocaine place themselves at a 40-fold increased risk of developing acute dystonic reactions to antipsychotics. (J.Milstein, 2013)

The patient cited in this case report is a young male, with a history of alcohol and nicotine use.

**STEP TWO: DETERMINE THE DIAGNOSIS:**
If the patient truly has Dyskinesia, then it is also imperative to determine the onset type; acute onset or tardive onset. Psychotropic medication-induced movement disorders (dyskinesias) are generally divided into these two groups based on the onset of abnormal involuntary movements. In this classification, (J.Milstein, 2013) Acute Dyskinesias develop within days, whereas Tardive (late) Dyskinesias may take as long as up to 6 months or more to manifest after exposure to the offending agent.

The patient in the case report appeared to have an acute onset of dyskinesia following use of Duloxetine.

**STEP THREE: DETERMINE TYE OF DYSKINESIA; FOCAL OR GENERALIZED?**
Focal dystonia generally involves the face or neck, and typically presents with blepharospasm, oromandibular dystonia, platysmal contractions, and emotional disabilities that have been reported to be associated with varying degrees of laryngospasm, and spasmodic. Generalized Dyskinesias are not limited to the above patterns, although they are also associated with emotional disturbances.

The patient in our case report, presented with symptoms indicating Acute Onset Focal Oro-Mandibular Dyskinesia.

Oro-mandibular dystonia consists of prominent contractions of the lower facial muscles and jaw muscle it is important to differentiate between Oro-Mandibular Dystonia and Oral-Buccal-Linguat Dystonias (of Tardive Dyskinesia) Although not definitive, it can be at times be distinguished from tardive dyskinesia by the symmetric involvement and absence of tongue protrusions. (Görkem Karakaş Uğurlu, 2013) (J.Milstein, 2013).

**MANAGEMENT:**
Management of Dyskinesia start methodically. Usually the first step is to stop the potentially noxious agent/offending agents. In the case in review it could have included Geodon, Adderall, and/or Duloxetine.

Following the discontinuation of the offending agent, supportive therapy and medication regime is initiated.

The treatment regime initiated for the case in review, is the Puget Sound Psychiatric Center Dyskinesia Treatment Protocol (PDTP) utilized at the Puget Sound Psychiatric Center. (Syed Jamal Mustafa, 2002). The details of the protocol is beyond the scope of this case review.

The PSPC Dyskinesia Treatment Protocol calls for an aggressive approach with medications; Benzodiazepines, Benztropin, Gabapentin and Vitamin-E.

**BENZODIAZEPINES:** Patient was started on Ativan (Lorazepam) for four weeks that was later switched to Diazepam. The Diazepam taper off, later on, was relatively smooth due to its long half-life and milder withdrawal symptoms. Benzodiazepines were started with rationale of having multiple actions such as anxiolytic, muscle relaxant, anticonvulsant and sedative-hypnotic effects that will be helpful in treating movement disorder.

The mechanism of action of benzodiazepines involves modulation of GABAergic activity by acting on the GABA—benzodiazepine—Cl complex, known to contain multiple modulatory binding sites and many receptor subtypes. (Seiji Nishino, 2009)

Care has to be taken when prescribing Benzodiazepines because of patient’s history of alcohol dependence, currently in early remission.

**BENZTROPINE (COGENTIN):** Dystonia is thought to be triggered by imbalance between dopamine and acetylcholine at nigrostriatal pathway. (Benjamin James Sadock, 2007). Some psychotropic medications (especially antipsychotics) decreases dopamine and may increase acetylcholine. Anticholinergic medications such as Benztropine Mesylate (Cogentin) was used to counter this cholinergic effect.

**GABAPENTIN (NEURONTIN):** Gabapentin has been used off-label for numerous conditions, including movement disorders (like ALS, essential tremors and Parkinson disease) anxiety, mood stabilization, alcohol withdrawals, sleep disturbance. The wide range of indications, few side effects and minimal drug-drug interactions make it a good choice for symptom control in our patients.

Gabapentin increases brain GABA by an amino acid active transporter at the blood-brain barrier. Gabapentin increases intracellular GABA by multiple enzymatic regulatory mechanisms. It increases the synthesis of GABA by increasing activity of glutamic acid decarboxylase and decreases GABA degradation by inhibiting GABA-transaminase. (Seiji Nishino, 2009)

**VITAMIN E:** Vitamin E is an antioxidant that binds with free radicals possibly produced by chronic use of psy-
CONCLUSION:

From this case it can be easily inferred that involuntary movements can develop for a variety of reason, and very rapidly at times. Once developed they lead to a great deal of anguish and agony both for the patient and their family and also for the treating Physician.

The unpredictable nature and uncertain outcome despite the best of treatment approaches further enhance the stress experienced by everyone involved in the treatment and management of such cases.

It should be emphasized that, because of the great variability in Dystonia, there are no universally accepted standardized successful guidelines to treat the acute dystonias, or those that may go on to become chronic.

Chances that a physician will encounter situations in which their patient will develop movement disorders is great and the odds continue to increase as exposure of our patients to various risk factors increases. Although the exact numbers are not available, it is fair estimation to consider that the risks might be almost approaching the same rate/ratio seen when the earlier generation anti-psychotic medications were used. One reason for predicting such a high rate is based on the sheer number of anti-psychotic prescriptions written in the current era as compared to the past.

The treatment approach used by the authors in treating this patient was the Puget Sound Psychiatric Center Dystonia Treatment Protocol, the patient was fortunate that the treatment protocol in his case was successful, with good results. However the real-worl limitation is that not all results are perfect, and more understanding and research needs to be conducted to continue to create better treatment protocols.

Apart from the medication aspect of the Treatment Protocol, other factors that are equally important in successful outcome include, (i) strong family support (ii) supportive psychotherapy (iii) frequent phone contact (iv) frequent office visits and examinations, and (v) positive and optimistic outlook by the treating doctor. One key aspect to remember is that patients who are resistant to treatment need to be identified early and alternate treatment plans discussed.

Clinicians, especially primary care physician, need to remain aware of the fact that even the so called benign antidepressant medications can cause dystonias. And that this particular side effect should also be discussed with patients along with other side effects before starting such medication. Additionally, providers need to be careful about drug-drug interactions in this era of poly-pharmacy.

Baseline and six-monthly examination for abnormal involuntary movement disorders should be considered for all patients who are on medications with high risk of involuntary movements. Checking drug interactions and educating patients and families about benefits as well as being honest about potential adverse effects is absolutely essential. It is also important that alternate treatment options need to be discussed so that informed decisions are made by the patients. This approach increases patient participation in decision making. It is also important to identify and address any adverse effects as early as possible.

References:


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