Suicidality Risk of Chronic Pain Medications

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Chronic pain is one of the main leading causes of disability in the world at present. A variety in the symptomatology, intensity and duration of this phenomenon has led to an ever-increasing demand of pharmacological treatment and relief. This demand for medication, ranging from well-known groups, such as antidepressants and benzodiazepines, to more novel drugs, was followed by a rise in safety concerns of such treatment options.

drug safety chronic pain suicidality opioids

1. Introduction

Current research estimates that 1.9 billion [1] individuals, and perhaps up to 30% [2] of the world's population, suffers from chronic pain, which is a leading cause of disability globally [3]. Although defined as pain that persists or recurs for longer than 3 months, the taxonomy [4][5] of chronic pain conditions has evolved as the clinical and scientific understanding of the syndromes and diseases that comprise the condition have grown. At present, chronic pain is understood to be a form of chronic disease, underpinned by nociceptive, neuropathic, and nociplastic mechanisms that can overlap, and/or exist on a continuum [2].

The clinical symptomatology and syndromes [4] of chronic pain are as heterogenous as the pathophysiological process underpinning them and as varied as the pharmacological attempts to alleviate them. NSAIDs, opioids, benzodiazepines, gabapentinoids, multiple generations of antidepressants, steroids, and antipsychotic medications are all utilized as treatments [6]. Many of these medications, irrespective of the indication they are being used for, have well documented associations with self-harm, suicidality, and overdose [7][8][9][10]. This is further complicated by the association and comorbidity that exists between chronic pain and psychiatric conditions, such as depression [11], bipolar disorder [12], and schizophrenia [13], which are associated with self-harm, suicidality [14][15], and overdose [16] themselves. Additionally, these patients may only experience relief from their symptoms when using these medications, some of which have a well demonstrated addictive potential [17][18]. The totality of these factors renders this population vulnerable to both intentional and unintentional misuse if their medications naturally pose drug safety concerns.

Given this reality, therapeutic drug monitoring and pharmacovigilance are of the utmost importance in this patient population. In 2018, an interdisciplinary group of clinicians developed consensus-based recommendations regarding urine drug monitoring for chronic pain patients who are treated with opioids [19]. While the combination of urinary drug testing and immunoassays has been found to be appropriate in some studies [20], others concluded that immunoassays designed to detect opioids lack sensitivity and produce false negative results in up to 21% of

cases [21]. These difficulties have been described in the case of therapeutic drug monitoring of benzodiazepines [22] as well. The current lack of effective, large-scale programs combined with the disruption in point of care monitoring during the pandemic has hindered progress in the realm of drug safety for chronic pain patients.

2. Socio-Demographic Characteristics

The socio-demographic parameters associated with a higher incidence of chronic pain are well known and established, with the main groups being age, sex, education, and marital status as well as socio-economic standing [1][23].

Age has consistently been a proven important risk factor for the development of chronic pain. Different studies suggest a wide range of prevalence of chronic pain amongst the elderly [24][25]. However, all are in agreement that the prevalence in the elderly is significantly higher compared to the younger population [26]. In addition, age has been reported as a specific risk factor for high-impact chronic pain [27].

Men are less likely to report the experience of chronic pain than women [28]. Similarly, women are more likely to seek diagnosis and treatment compared to men, which could in turn cause possible misleading statistics [29]. Women have a tendency to maladaptive coping strategies to pain, predisposing them to a possibility of developing chronic pain [30].

In women, schooling of 12 or more years was associated with a lower prevalence of chronic pain. In the same light, unemployed women show a higher prevalence of chronic pain compared to their employed counterparts. Marital status showed influence on both sexes, where an increased prevalence of chronic pain was noted in divorced or widowed women; yet, conversely, it decreased in single men compared to married, divorced, or widowed men [31].

Chronic pain is a well-established follower of lower socio-economic status and a poorer quality of life [32]. Those who are socio-economically deprived are not only more likely to experience chronic pain but also more likely to experience more severe pain and a greater level of pain-related disability [33]. It has also been shown that average pain intensity and pain-related disability was greater among African American than White respondents, and it decreased as wealth increased [33].

When it comes to suicidality and chronic pain, a review of the currently available literature reveals a myriad of research suggesting that suicidal ideation and suicidal attempts are more common in patients with chronic pain [34]. In addition to that, although assumed logical, patients with painful conditions are at a greater risk of suicide compared to patients with non-painful conditions [35].

Well-known risk factors for suicide in the general population include family history of suicide, previous attempts, comorbid depression, and female sex [36][37]; however, less is known for pain-specific risk factors.

Patients with simultaneous chronic pain and substance use disorders (SUDs) are a more complex topic. Physicians must focus on both chronic pain treatment as well as issues of medication safety and misuse. The data suggest that the current prevalence of SUDs amongst patients with chronic pain ranges from 3% to 48%, and that the lifetime SUD rate is somewhere between 16% and 74% [38]. Additionally, up to 11.5% of chronic pain patients that take opioids develop aberrant medication-related behaviors [39]. Other studies suggest that patients with chronic pain have a 2 to 3 times more likely chance of developing SUDs, compared to individuals without pain [40].

3 Pharmacological Treatment and Suicidality

3.1. Antidepressants

Overall, the use of antidepressants has increased in recent decades, with SSRIs leading this trend change since their discovery [41][42].

Though not the main indication, one of the treatment options for chronic pain have historically been antidepressants, with TCAs, SSRIs, and SNRIs being in the forefront of therapeutic options [43][44]. Patients with chronic pain are often treated for a prolonged period of time, usually with more than one type of medication [45], all of which have a vast side effect profile [46]. These factors, in combination with the psychological strain that these patients are exposed to [47], can lead to a mental state prone to suicidal thinking and ideation [48][49].

A variety of information currently exists on the topic of suicidality rates in correlation to antidepressant use, suggesting negative, positive and no correlation at all [50][51][52][53]. Randomized controlled trials (RCTs), baring the highest level of evidence, showed contradictory results, ranging from a significantly increased suicide risk while using antidepressants [54][55][56][57] to seemingly no change in such risk [58][59][60]. Nonetheless, the vast amount of literature showing that a relationship between these parameters might exist is worth mentioning.

Additionally, a 2009 study showed a highly age-dependent relationship between the use of antidepressants and suicidality. The research showed that young adults (aged 25 and younger) showed a higher suicidality rate on these medications, in adherence with findings in children and adolescents. Conversely, the use of antidepressants in adults (aged 25 and older) showed a protective factor against suicidality [60]. This discrepancy in response to the initiation of antidepressant treatment was later reproduced many times in the literature, further supporting the caution of prescribing these medication to children and younger adults [59][61]. However, it is of high importance to mention that, with an increased risk of suicide in untreated depression and no concrete proof of association between pharmacotherapy and changes suicidality, physicians are still urged to prescribe SSRIs to affected minors [50].

The time of onset of suicidality in relation to depression treatment is of key importance to understanding the possible connection between these states. Suicidal ideation and behavior can initially develop during depression treatment, expressed by the term treatment-emergent suicidal ideation (TESI). In the case of the already present suicidality that changes in intensity in reaction to treatment, the term treatment worsening of suicidal ideation

(TWOSI) fits best [62][63]. Even though these terms have been linked to a poorer socio-economic status and genetic predisposition [63][64][65], the literature suggests that more research is needed to conclude such a relationship. Some nation-based studies have reproduced this correlation between the use of antidepressants and the onset of suicidal attempts [66][67].

3.2. Opioids

Among all the medication classes, opioids by far have received the most attention from the public in recent years. The socio-economic factors that are related to opioid use may directly contribute to the inherent risk of suicide with opioids. It has been theorized that the diminishment in the middle class and the general economic stress of workers has led to a use of opioids as a coping mechanism [68]. Furthermore, patients who are on opioid medications for extended periods of time have significantly increased risks of developing depression [69][70]. Both the relationship of opioid use with hardship, as well as the relationship between use and developing depression, seem likely candidates as the causes of opioid-related suicides.

The national center on health statics reported 80,311 overdose deaths involving opioids in 2021, about 75.4% of all lethal overdoses [71]. In October 2017, the opioid crisis was declared a public health emergency by the US government. The CDC reported that, in 2020, about 143 million prescriptions were written in the United States. This follows a general trend of declining prescriptions in the USA since 2012 [72]. While the general trend of declining opioid prescriptions may mean that certain communities are less encumbered by the societal burden of treating addiction, this effect is very clearly disproportionately applied across the USA. The CDC makes note of county-level trends that are extremely different than the nationwide averages, with certain counties reaching prescription rates (per 100 persons) up to nine times higher than the average (43.3 prescriptions per 100 persons) [72].

Prescription maps of the USA illustrate these trends, showing the dramatic patchwork of opioid prescription rates across the country. There are multiple theories that attempt to specifically define the risk factors that these areas share. Theories include income, race, and density of people (rural vs. urban development).

Regarding the effects of community structures and opioid misuse, a 2020 study investigated the relationship of income inequality and opioid prescription rates. The authors specifically investigated the variables of residential stability, defined as the level of connectedness between residents as assessed through people staying housed in the same place, as well as the variable of social isolation among individuals [73]. The authors were able to quantify these variables in a couple different ways. The Gini index was used as a measure of income inequality, residential stability was defined by the percentage of housing occupied by owners, and social isolation was indexed via the percentage of individuals who are disabled, the percentage of individuals who live alone, and those living in poverty. These variables were chosen as the demographic studied was those enrolled in Medicare, a program only available predominately to those above 65 years old, or with end-stage renal disease, amyotrophic lateral sclerosis, and those with severe disabilities. The authors found that high levels of income inequality are associated

with low levels of residential stability and high levels of social isolation. Both variables in turn are related to more opioid prescriptions [73].

These conclusions across the last few paragraphs can be further related to the fact that income inequality has a correlation to depression and suicidality [74]. As these papers have shown, these inequities lead to more opioids being used, and there are likely going to be more completed suicides due to the relationship between access to a highly lethal suicide means and completion [75].

Looking beyond economic factors, sex differences are also quite profound in opioid-related suicide. In general, women attempt suicide at greater rates then men but die by suicide at significantly lower rates. In the context of opioid-related suicide, a large cross-sectional study found that women comprise 54% of lethal suicides with opioids [76]. This may be further contextualized by a higher incidence in concomitant mental health complaints among women being treated for opioid dependence [77], as well as women with opioid use disorder reporting usage to cope with negative emotions at a higher rate [78]. Of note, the overall intentional overdose rate for all medications decreased between 2012 and 2019, but increased among African American women [79]. This may be a reflection on the general change in demographics that comprises the opioid crisis in the USA.

It has been noted that there is a multifactorial incidence of lower access to psychiatry in minority populations [80][81][82], along with lower rates of naloxone access in minority populations. Therefore, it is possible that, among minority patients who intentionally overdose and are not revived, more suicides will be misclassified as unintentional deaths. In a population study of New York City opioid users, researchers found significant differences in naloxone use and training. The data showed that African American participants had a 0.4 odds ratio of naloxone training, African American people above 50 years of age had an odds ratio of 0.2, and African American women scored 0.27 compared to White women [83].

3.3. Gabapentinoids

The antiepileptics gabapentin and pregabalin are routinely used for the treatment of chronic neuropathic pain, and particularly diabetic neuropathy. While systematic reviews have validated their efficacy [84][85], experts are increasingly concerned about how ubiquitous their use has become [86]. By 2016, 64 million prescriptions were issued for gabapentin, making it the 10th most prescribed drug in the US market. This constitutes a rise of over 160% compared to 2012. Pregabalin sales generated USD 4.4 billion in 2106, more than doubling the sales value since 2012 [86]. This phenomenon was simultaneously occurring, with different magnitudes, across the world.

While the prevalence of conditions treated with these medications continues to increase, the opioid epidemic was equally, if not primarily, responsible for the increase in physicians prescribing gabapentinoids. Although the most common side effects of antiepileptics are well documented, dose-dependent, and reversible, the implication of gabapentinoids in drug misuse, self-harm, and suicidality has come into focus in recent years [8][86][87].

The association between antiepileptics and suicidality was described by multiple systematic reviews, prompting the FDA to issue a warning for 11 drugs, including gabapentin, in 2008. However, despite a growing body of literature

on the topic, gabapentinoids are not considered controlled substances in Europe, Canada, Australia, or the United States at the federal level, although some states have begun to reclassify them individually [88].

3.4. Benzodiazepines

As previously mentioned, chronic pain patients are often polypharmacy patients, managing their symptoms with several treatment modalities. Especially in the United States, opioids take the main place in the treatment options for chronic pain [89]. However, the co-administration of benzodiazepines with opioids has been a prominent pain relief strategy for these patients [90][91][92], leading to concerns surrounding interaction and adverse-event amplification when used concomitantly [93][94][95][96][97][98]. A study found that patients with a co-prescription of opioids and benzodiazepines were more likely to be diagnosed with depression, PTSD, and bipolar disorder and were more likely to be prescribed additional medication, such as antidepressants [99].

The most common conditions that are primarily treated with benzodiazepines that are linked to possible suicidality are anxiety and insomnia [100][101]. Treating these conditions would lead to a logical decrease in suicidality, but what happens when the treatment option itself is a possible risk factor for suicide?

Various instances in the literature suggest a very strong association between the use of benzodiazepines and suicidality and suicide attempts. However, many of these studies fall under possible indication bias, linking the condition being treated to possible suicidality rather than the pharmacological treatment option itself [102][103][104][105][106]. Minimizing such biases, by using cohorts [107][108][109] and case–control studies [110], yielded similar positive correlations.

Benzodiazepines have been shown to increase aggression and impulsivity [111], both of which appear to be correlated to suicidal tendencies [112]. Recent studies showed a dose-dependent relationship with the incidence of suicidality, both in short- and long-term benzodiazepine use [104][108][113][114].

3.5. Other Medication Groups

3.5.1. Barbiturates

The combination acetaminophen/butalbital/caffeine pill uses the analgesic effects of acetaminophen with the barbiturate butalbital and caffeine for the treatment of tension headaches. A tension headache is a type of headache that causes pain in a band around the head bilaterally [115]. Out of all the medications studied in a 2019 paper, the combination acetaminophen/butalbital/caffeine pill was associated with the highest odds ratio of suicidal event increase after exposure, 1.68 (95 CI 1.16–2.44), with the paper able to study 1,154,666 patients that were prescribed this combination [116]. Headaches are one of the most common forms of pain, both acute and chronic. About 15.8% of the global population experiences headaches each day [117]. More specifically, a population study conducted in Denmark found a prevalence of chronic tension headaches at 2–3% [118].

The combination acetaminophen/butalbital/caffeine pill has been shown to be effective at anxiolysis in the tension headache population [119]. Although the pathogenesis of tension headaches has not been fully elucidated, there is likely a relationship with mental health diagnosis, with one study showing an 84% overlap in patients with tension headaches and psychiatric diagnosis [120]. This masking of psychological symptoms along with analgesia creates a risk of over usage in times of stress, in turn raising the risk of both overdose as well as a possible withdrawal-associated psychiatric crisis [121]. Barbiturate prescriptions have been on the decline for decades, but prescribers should be vigilant in monitoring patients for comorbidities as well as medication misuse.

3.5.2. Cyclobenzaprine

Cyclobenzaprine is a skeletal muscle relaxant marketed for the use of musculoskeletal pain and/or spasms, although it is also used for the treatment of fibromyalgia off-label [122]. A 2019 study that found that the association between cyclobenzaprine and suicide had an odds ratio of 1.34 (95% CI 1.06–1.68) with 7,487,505 patients. Of note, the study found a smaller risk of suicidality in men compared to women, with an odds ratio of 1.21 (0.96–1.58) vs. 1.39 (1.13–1.71), respectively [116].

3.5.3. Prednisone

Prednisone is a glucocorticoid medication used for a wide variety of pathologies. By decreasing inflammatory responses in the body, steroid medications can help with many painful rheumatic conditions. Prednisone was found to carry an overall odds ratio of suicidality of 1.33 (1.10–1.61), with higher rates in men 1.42 (1.07–1.88) vs. women 1.33 (1.08–1.64). The paper was able to study 10,667,620 patients [116]. Two commonly cited papers assessing the incident rate of psychiatric events in patients treated with steroids described a rate of severe psychiatric adverse events at 6% in patients treated at high doses, while another cohort study found an incidence of mania or depression as high as 36% among patients treated with high-dose steroid regimens [123][124].

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