Clinical Research on Foot & Ankle
ISSN: 2329-910X

Review Article Open Access

Risks and Outcomes of Extremity Fractures in Patients with Known Mental Health Disorders: An 'Ortho-Psychiatric' Perspective and a Systematic Review of the Literature

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Abstract

Objective: We aim to review the risks and outcomes of fractures in patients with pre-existing mental health disorders.

Methods: Articles published in the English language from Jan 2000 to March 2020 were searched through PubMed, Ovid, Embase, ScienceDirect and ISI Web of Knowledge. Medical Subject Headings (MeSH) terms were used along with text words. Applying the inclusion and exclusion criteria, of the 390 searched articles, 13 were included for final analysis in line with recommendations from PRISMA guidelines.

Main Results: Total participants from all these studies were 1,11,61,087 with a combined mean age of 51.4 years. Two-thirds of the participants were females. The combined mean of fractures and falls was 61.8% among all participants in included studies. The combined mean incidence of mental health disorders was 74.3% among all participants with fractures. Use of psychotropic medications was found to be associated with impairment of cognition, psychomotor function and bone mineral density leading to a substantial increase in fracture risk.

Conclusion: Patients with fractures and underlying mental health disorders were reported to have a prolonged hospital stay, poor functional outcomes and increased risk of chronic pain syndrome. Strategies should be in place for early identification of psychiatric disorders following a fracture to mobilize psychosocial support and facilitate discharge.

Keywords: Mental illness; depressive illness; Schizophrenia; Fractures; Limb injuries

Introduction

The incidence of fractures as well as of the mental health disorders among the general population is on the rise due to various dynamic epidemiological factors [1,2]. As separate entities, there are challenges in the management of orthopaedic trauma under any given circumstances, as well as, there are remarkable challenges in the management of mental illnesses faced by the respective specialties. The existence of fractures in patients with underlying mental health disorders not only amplifies these challenges for treating clinicians but also multiplies the expected utilization of the available healthcare resources [3]. According to recent epidemiological statistics, mental health disorders and musculoskeletal disorders collectively account for over 30% of the global years lived with disability [4]. A study making a careful estimate suggested that by 2030, the worldwide number of individuals with mental health disorders is expected to double [2]. The available evidence suggests a higher risk of sustaining orthopaedic injuries in patients with underlying mental health comorbidities [5,6]. This is not only due to the nature of the psychiatric condition itself but also due to the psychotropic medications used for their long-term treatment and the resultant combined negative effect on bone mineral density (BMD) [3].

Studies have reported a high incidence of psychiatric disorders in the elderly hip fracture population with a prevalence of 9–47% for depression and 31–88% for cognitive impairment [7,8]. Traditional management of orthopaedic trauma is centered around stabilization of the injured limb and restoration of physical function back to the pre-injury status. It has been reported by the mental health clinicians that the functional consequences of orthopaedic problems in patients with known mental health disorders may be under-appreciated by non-mental healthcare providers [9]. Therefore, the pre-existing mental health issues may not obtain sufficient attention during post-surgical rehabilitation and may negatively impact on the clinical and functional outcomes of the orthopaedic injury [3]. There are several studies in the current literature that have demonstrated worse outcomes following elective orthopaedic procedures, however, there is a paucity of literature evaluating the outcomes of orthopaedic trauma with pre-existing mental health disorders. We hypothesized that the presence of a pre-existing mental health diagnosis is associated with higher risks of sustaining limb fractures and poor outcomes of their management. We aimed to review the available literature and explore this hypothesis from an orthopaedic and psychiatric clinicians' perspective.

METHODOLOGY

Search strategy

A literature search was conducted through the databases including PubMed, Ovid, Embase, ScienceDirect and ISI Web of Knowledge. Articles published from January 2000 to March 2020 were searched. The search was limited to articles available in the English language only.

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Received May 30, 2020; **Accepted** June 22, 2020; **Published** June 29, 2020

Citation: Saeed U, Majeed H (2020) Risks and Outcomes of Extremity Fractures in Patients with Known Mental Health Disorders: An 'Ortho-Psychiatric' Perspective and a Systematic Review of the Literature. Clin Res Foot Ankle 8: 295

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Search terminologies

The National Library of Medicine's (NLM) Medical Subject Headings (MeSH) terms were selected and used along with text words. The terminologies that were used, included "Orthopaedic Injuries" OR "Fractures" OR "Musculoskeletal Injuries" AND "Mental Disorder" OR "Psychiatric Disorders" OR "Depressive Illness" OR ''Eating Disorders'' OR "Schizophrenia" OR "Bipolar Disorder". MeSH terms provided a consistent way to retrieve information where different terms had been used by authors for the same concept.

Inclusion criteria

All types of articles reporting on extremity fractures and orthopaedic injuries in skeletally mature patients with underlying mental health disorders were included. Articles reporting on all types of mental health diagnoses were included. Articles with open and closed fractures were included.

Exclusion criteria

Articles were excluded if related to fractures other than limb fractures (spinal injuries, skull fractures, rib fractures and maxillofacial injuries). Articles in languages other than English were also excluded.

Quality appraisal and analysis

The study was performed following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). The PICO method (Population, Intervention, Comparison and Outcome) and CASP tools (Critical Appraisal Skills Program) were used to appraise the quality of selected studies and analyze their results [10,11]. Both the authors (US, HM) performed the literature search and reviewed the titles and abstracts in the first phase. Based on this information, articles that were deemed to meet the inclusion criteria were identified. Full texts of these articles were retrieved electronically and reviewed fully in the second phase. In the event of any discrepancy between the two authors, mutual discussions lead to a consensus with no disagreements. Data were extracted by systematic analysis of each article and summarization in Microsoft Excel® version 2019 (Microsoft, Redmond, WA, USA). Chi-square tests were utilized to calculate p-values. A p-value of less than 0.05 was considered significant.

Results

The literature search identified 325 articles in the first phase through the search databases. Sixty-five additional articles were identified through citation sources of the selected articles. After screening for duplicates, 345 articles were screened. After applying inclusion and exclusion criteria, 23 suitable articles were identified for full-text review. Another 10 of these articles did not fulfil the study criteria and were excluded. The authors reached a consensus for 13 articles for final inclusion and analysis. Figure 1 presents the PRISMA flow diagram of the screening and selection process. The characteristics of the included studies are presented in Table 1.

The combined total participants included in all these studies were 1,11,61,087 (range: 62 to 10,669,449) with a combined mean age of 51.4 years (range: 14 to 82 years). The study duration ranged from 3 months to 21 years. Among all the studies, most participants were females (65%). The total weighted mean of fractures and falls was 61.8% among all the participants in all the included studies (6.4% to 100%). The total weighted mean incidence of mental health disorders in patients with fractures was

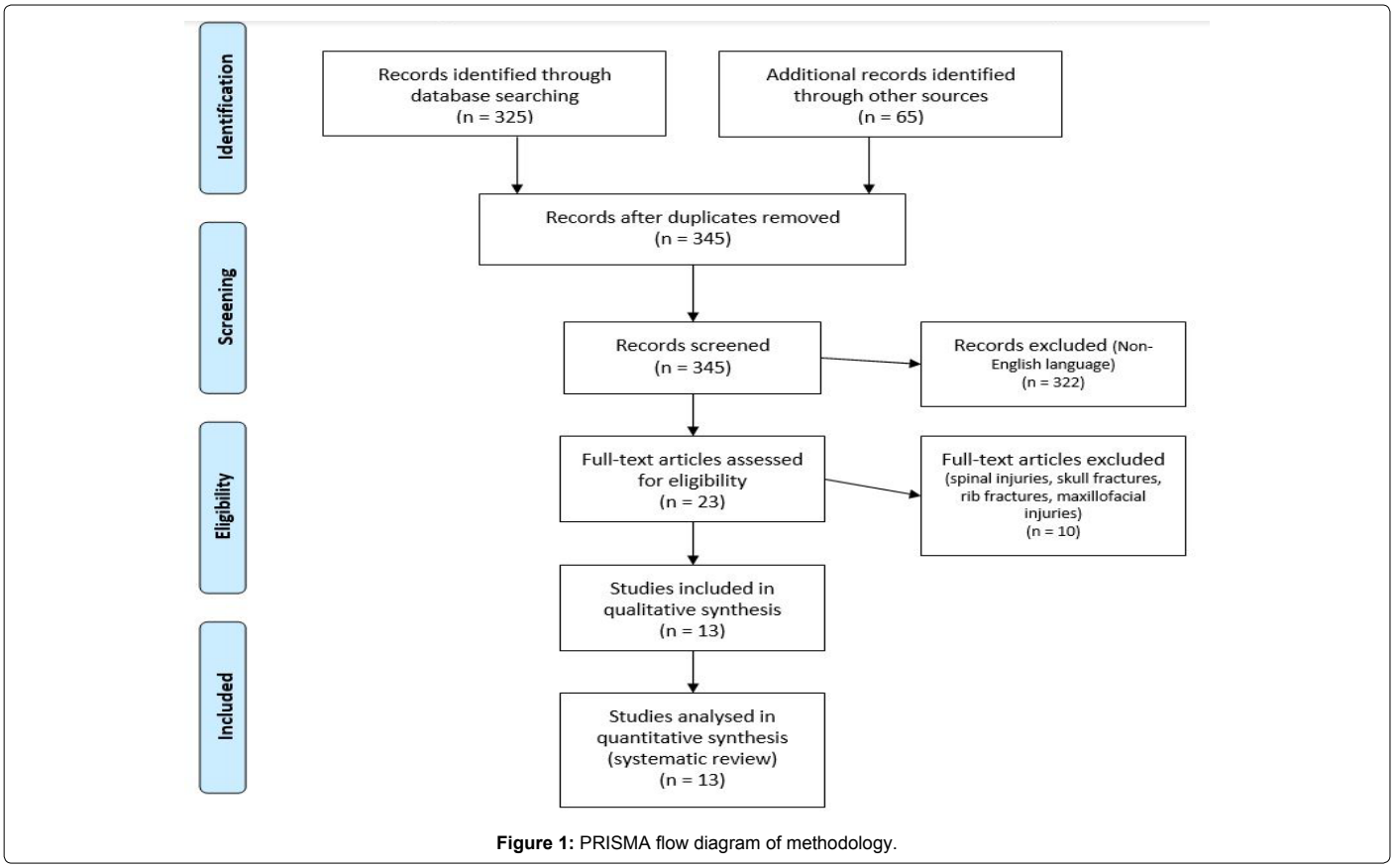

Figure 1: PRISMA flow diagram of methodology.

Authors	Year published	Type of study	Duration of data [years]	No of patients	Male	Female	Mean age [years]
Frolich et al. [20]	2020	Retrospective	10	803	0%	100%	19
Simske et al. [3]	2019	Retrospective	13	1378	72%	28%	43
Zachwieja et al. [18]	2019	Retrospective	18	267,897	19%	81%	77
Stubbs et al. [22]	2018	Retrospective	7	11,567	57%	43%	43
Sharma et al. [21]	2018	Retrospective	2.5	8036	36%	64%	81
Vincent et al. [28]	2018	Prospective	10	6353	62%	38%	45
Schwartz et al. [16]	2018	Retrospective	10	139,450	26%	74%	64
Su et al.[17]	2017	Retrospective	17	3705	38%	62%	43
Hsu et al. [14]	2016	Retrospective	8	47271	38%	62%	43
Menendez et al. [15]	2013	Retrospective	18	10,669,449	36%	64%	67
Wood et al. [27]	2011	Retrospective	0.4	62	47%	53%	39
Vestergaard et al. [23]	2002	Retrospective	21	4385	5%	95%	23
Holmes et al. [26]	2000	Prospective	2	731	18%	82%	82

Table 1: Demographic data of the included studies.

74.3% among all the participants combined in all the included studies. The details of mental health diagnoses are presented in Table 2.

Psychiatric diagnoses were based on the criteria derived from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes [12] in 6 studies [13-18] and ICD-10 [14,15,19] in 4 studies [20-23]. Diagnoses were derived from the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria [12,24] in one study [3], from the community version of the Geriatric Mental State (AGECAT) [25] in another study [26] and one study did not provide this information [27].

Delayed discharge after fractures

Nine studies reported the association of hip fractures with mental health disorders [14-18,21,22,26,28]. Holmes and House reported that patients with dementia, delirium and depression had a longer hospital stay and a significantly higher rate of discharge to a non-home destination (21.4% vs 2.2%, $p<0.001$) than the patients without any mental illness after hip fractures [26]. Presence of psychiatric illness also significantly increased physical dependence after hip fractures. The relative risks of mortality over 6 months after hip fracture were significantly higher in patients with dementia and delirium as independent risk factors after adjustment for age, gender, fracture type, residential status, deprivation score and physical illness, but depression did not have a significant effect on survival at 6 months.

Menendez et al. found that hospital stay after hip and other lower limb fractures was longer in patients with schizophrenia and dementia compared with patients without any mental disorders but shorter in patients with depression and anxiety [15]. Significantly higher number of patients were discharged to a care facility (dementia: 63%, schizophrenia: 55%, depression: 41%, anxiety: 34%). Patients with mental disorders had significantly more adverse events compared to the control group ($p=0.001$). Patients with schizophrenia (31%) and dementia (33%) had more adverse events than those with depression (24%) and anxiety (25%). Depression was the only diagnosis found to be associated with higher rates of blood transfusion (14%). However pre-existing psychiatric comorbidity was not associated with a higher risk of in-hospital death after a lower limb fracture.

Stubbs et al. investigated the predictors of falls and fractures leading to hospitalization with pre-existing schizophrenia-spectrum disorders [22]. Of a total of 822 patients, 14 (0.12%) died following the injuries sustained after a fall and 28 (0.24%) died following fractures. In multivariable analysis, increasing age, white ethnicity, analgesics, cardiovascular disease, hypertension, genitourinary disease, visual disturbance, syncope, and previous history of fracture were significant risk factors for both falls and fractures. The average no of days of inpatient stay was 10.8 days after a fall and 20.2 days after a fracture in these patients.

Sharma et al. investigated the risk of falls ad fractures in patients known to suffer from dementia and reported that over an average of 2.5 years, nearly half of these patients suffered from a fall or a fracture leading to hospitalization [21]. Of 8036 people with dementia, 2500 (31%) had a fall and 1437 (17.7%) had a fracture. In multivariable models, significant predictors of falls were observed to be increased age, female gender, physical health problems, previous fall or fracture, vascular dementia, non-cohabiting status, and problems with living conditions.

Schwartz et al. reported that psychiatric comorbidity adversely affected the length of stay, adverse events, and inpatient mortality ($p<0.001$) after sustaining lower limb fractures, in particular among the low socioeconomic group [16]. Length of hospital stay was 7 or more days in 33.5% of patients with mental illness compared to 27% in patients without it ($p<0.001$). Rate of adverse events was 12.8% in patients with mental illness compared to 9.6% in the others.

Su et al. reported that bipolar patients had significantly higher risk of fractures when compared to matched controls (17.6% versus 11.7%, respectively, $p<0.001$) [17]. A higher cumulative dose of antipsychotics or mood stabilizers did not seem to increase the risk of fractures. Other factors, such as female gender, older age, substance abuse and diagnosis of osteoporosis, were associated with a higher risk of fractures. Patients with bipolar disorders living in urban settings and those with higher income were observed to be at lower risk of fractures.

Zachwieja et al. reported that the patients with hip fractures and underlying psychiatric illness had a significantly delayed discharge from the hospital and discharge to a non-home location ($p<0.001$), in particular schizophrenia (mean: 17 days) [18]. Rate of adverse events was significantly higher in patients with mental illness (21.7%) compared to other patients (17.7%) schizophrenia ($p<0.001$). Hsu et al. reported that patients with bipolar disorder had an 88% increased fracture risk compared to those without any mental health disorder [14]. The need for utilizations of healthcare facilities was observed to be 6-times higher in these patients than those without the bipolar disorder in their study.

Fracture risk in patients with eating disorders

Two studies reported an increased risk of orthopaedic fractures in patients with eating disorders secondary to the effects of malnutrition

Authors	Fractures and falls	Known psychiatric disorder [%]	Diagnoses
Frolich et al. [20]	13%	100%	Eating disorders [100%]
Simske et al. [3]	100%	17%	Depression [63%], Anxiety [23%], Bipolar disorder [14.5%], Schizophrenia [7.5%], Dementia [4%], Others [8%]
Zachwieja et al. [18]	100%	100%	Depression [37%], Anxiety [11.5%], Schizophrenia [6.4%], Dementia [49%]
Stubbs et al. [22]	7%	100%	Schizophrenia spectrum disorder [100%]
Sharma et al. [21]	50%	100%	Dementia [100%]
Vincent et al. [28]	100%	44%	Alcohol excess [18%], Illicit drug use [8.3%]
Schwartz et al. [16]	100%	25%	Dementia [14.3%], Depression [6.9%], Alcohol excess [2%], Substance misuse [0.9%]
Su et al. [17]	18%	100%	Bipolar disorder [100%]
Hsu et al. [14]	21%	100%	Bipolar disorder [100%]
Menendez et al. [15]	88%	8 %	Depression [3.2%], Anxiety [1.6%], Schizophrenia [0.6%], Dementia [2.9%]
Wood et al. [27]	100%	100%	Depression, Anxiety
Vestergaard et al. [23]	6.4%	100%	Eating disorders [100%]
Holmes et al. [26]	100%	72%	Dementia [40%], Delirium [15%], Depression [13%], Alcohol misuse [2%], others [2%]

Table 2: Incidence of mental health disorders and fractures in the included studies.

and low body weight. Frolich et al. found higher fracture risk (upper arm and hip) in anorexia nervosa but not in bulimia nervosa or other eating disorders [20]. Disease remission was associated with lower fracture risk compared to active disease, but higher fracture risk compared to the control group. In regression analysis, age at the onset, body mass index (BMI) and the overall duration of the disease before referral for treatment, all independently predicted fractures. They suggested that efforts toward early nutritional rehabilitation and weight gain might prove to be effective towards the reduction of fracture risk in these patients.

Vestergaard et al. analyzed the patients with known eating disorders from Danish registry and reported an increased fracture risk in anorexia nervosa from the time of diagnosis but not before, except for the risk of femoral fractures [23]. A significant increase in fracture risk was seen before the diagnosis of bulimia nervosa with a trend towards a further increase after the diagnosis was established. In individuals with eating disorders not otherwise specified, the risk of sustaining fractures was found to be significant before as well as after the time when the diagnosis was established.

Fracture risk in obese patients with mental health disorders

Two studies reported the risk and outcomes of fractures in obese patients with mental health disorders. Simske et al. reported that pre-existing mental disorders combined with obesity had major influence on secondary operation rates and functional outcomes following ankle fractures [3]. In their cohort of 1378 patients, the average BMI was 31 kg/m^2, and 43% were considered obese. Depression was the most common disorder (63%), followed by anxiety (23%) and schizophrenia spectrum disorders (8%). Mental illness was associated with older age, female gender (72%) and other medical comorbidities (diabetes and obesity, 48%). Incidence of complications was higher than the rest of the cohort but not statistically significant (15% vs 12%). The requirement of secondary operations (13% vs 7%) was significantly higher ($p<0.05$), most needed for removal of metal implants (8% vs 4%). Functional outcomes were significantly worse in mentally ill patients as assessed by Foot Function Index ($p=0.006$) and Short Musculoskeletal Function Assessment Mobility ($p<0.01$).

Vincent et al. analyzed the outcomes of obese patients (BMI>30 kg/m^2) with pre-existing mental health disorders following orthopaedic injuries [28]. Of a total of 6353 patients, 29% (1830) had BMI over 30 kg/m^2. Of these 44% (803) patients had a known history of mental health illness, illicit drug use and alcohol abuse. This group of patients had significantly longer stay in hospital and discharge destinations other than home after sustaining orthopaedic injuries.

Pain perception & functional outcomes after fractures with mental health disorders

Alluri et al. reported that the patients with a known psychiatric disorder were five times more likely to develop chronic regional pain syndrome (CRPS) after sustaining an ankle fracture ($p<0.001$) [13]. CRPS was identified in 6.2% (10,127) patients with a known psychiatric disorder. The disorders found most predictive of developing CRPS included delirium, bipolar disorder, and anxiety disorder. It was interesting to observe that surgical intervention did not pose any additional risk of developing CRPS in these patients ($p=0.31$).

Wood et al. reported that depression in combination with anxiety sensitivity contributed to a significant amount of the variance in pain scores [27]. The authors suggested that early screening of patients after sustaining orthopaedic injuries could identify those who might be vulnerable to develop persistent pain disorders. This could lead to early intervention using adequate psychiatric support and effective pain management to reduce the risk of acute pain evolving into a chronic pain disorder.

Discussion

To the best of our knowledge, this is the first systematic review to analyze the risks and outcomes of limb fractures in patients with underlying mental health illness. The included studies reported a high incidence of limb fractures in patients with all types of mental health diagnoses, which were associated with a prolonged hospital stay, poor outcomes and persistent pain issues. Majority of the studies reviewed the patients with hip fractures, which have been reported to account for most osteoporotic fragility fractures and over 40% of the estimated burden of osteoporotic fractures worldwide [29]. The combination of fractures and mental health disorders was observed to be more common in females and the elderly population. Psychological factors were reported to be capable of influencing an individual's perception of pain and mediating the evolution from acute to chronic pain syndrome. The pain was reported as one of the key drivers of anxiety, depression and post-traumatic stress disorder fostering catastrophizing behavior, either as new or worsening mental illness [30].

Pathophysiology of increased fracture risk with pre-existing mental health disorders

Different mechanisms have been described in the literature that could explain the association of increased fracture risk with underlying

mental disorders. Biological factors including inflammation, mitochondrial dysfunction, oxidative stress, and endocrine factors have common pathways that can affect neuroprogression in certain psychiatric disorders while simultaneously promoting bone loss through accelerated osteoclastic activity [31]. Elevated cytokine levels or neuroinflammation is associated with both mania and depression. Chronic neuroinflammation results in increased free radicals, decreased mitochondrial function, lipid peroxidation and excitotoxicity, which may lead to increased intracellular and glutamate levels resulting in a neuroprogressive effect [32]. There is sufficient suggestion in the literature that inflammation is a key mediator in the development of osteoporosis [33]. In addition to inflammatory process, disturbed hypothalamic-pituitary-adrenocortical (HPA) axis may be another hypothesis for association between certain psychiatric disorders and increased fracture risk. Dysfunction of HPA axis activity has also been shown to be associated with chronic psychological stress and increased risk of osteoporosis [14].

Old age is associated with reduced cognitive and motor function resulting in deficits in coordination, balance and gait predisposing the elderly to a higher risk of falls and fractures. Psychiatric disorders are associated with many poor health behaviors that lead to physiological consequences, which in turn have a negative effect on bone mineral density (BMD). Certain disorders lead to an increased incidence of smoking and alcohol use, which are associated with lower BMD by inhibiting estrogen activity and calcium absorption, and inhibition of bone cell proliferation and function, respectively. These disorders are also associated with fatigue and reduced physical activity and the level of physical activity is directly proportional to BMD [31].

Association of psychotropic medications with the risk of fractures

The available evidence in the literature suggests that psychotropic medications result in impairment of cognitive and psychomotor function, balance and gait, and impair the bone mineral density leading to a substantial increase in the risk of falls and fractures [34-39]. The use of first-generation antipsychotics has been related to a higher risk of fractures compared to second-generation of these drugs [40]. There are two possible mechanisms by which psychotropics may exert an increased risk of hip fractures: firstly, by increasing the risk of falls, and secondly, by increasing the probability that when a fall takes place, it will result in a fracture [41]. Regardless of the cause, when an elderly person falls, the maximum force of the injury exerts on the neck of the femur leading to a high risk of fracture, which multiplies with pre-existing osteoporotic changes due to multifactorial etiology. Table 3 summarizes the studies that have reported the association of psychotropic medications with fractures.

The potential moderating effects of lithium on the risk of fracture have resulted in conflicting findings in the literature. In a study by Lewicki et al., lithium was found to be associated with bone loss in healthy rats after three months of exposure [42]. In contrast, a clinical study in patients with known mental health disorders reported that one year of maintenance therapy with lithium was associated with elevated bone mass [43]. The authors of two other population-based case-control studies reported a decreased fracture risk with the use of lithium [44,45]. However, the protective effects of Lithium on bone density was not supported by a study performed on its users from the United Kingdom General Practice Research Database [17].

Strengths and limitations of the selected articles

The selected studies had large cohorts of participants with regards to the spectrum of known mental health disorders. Samples in most of the studies were drawn from large national health insurance and administrative databases had a diverse sample of patients, heterogeneity of the injuries and patient characteristics, which make these findings generalizable to a larger orthopaedic trauma patient population.

When interpreting the limitations of the included studies, several inherent issues, and risks of multiple biases from a retrospective analysis of large administrative databases should be kept in mind. The possibility for misclassification error could exist because the now-outdated ICD-9-CM system was used to retrieve diagnoses, procedures, and adverse events in 6 of these studies and the currently used ICD-10 criteria were used in only 4 of the included studies. Therefore, due to this fact, the conclusions drawn from the analyses may be somewhat misleading if the data were found to contain any errors in the coding process. In addition, a possible variation in diagnostic criteria from case to case in different clinical and cultural settings could have either increased or decreased the prevalence of the psychiatric diagnoses. However, this criticism may be mitigated by the large number of patients studied over many years in most of the studies. All but two studies [26,28] were retrospective, giving rise to potential flaws as the authors could only utilise the parameters that were available for assessment without a direct control on the data. In all the retrospective studies there was a high risk of observer bias, assessment bias, bias due to lack of power, and selection bias due to study design and incomplete outcome data.

Conclusions

Patients with pre-existing mental health disorders are at higher risks of sustaining limb injuries and fractures, not only due to the underlying diagnosis itself but also due to the impact of psychotropic medications used for its treatment. These patients have been reported to have a significantly prolonged hospital stay, poor functional outcomes and increased risk of chronic pain syndrome. Incidence of fractures was found to be higher with older age, female gender

Authors	Year Published	Type of Study	Studies Included	Type of Drugs Studied	Main Findings
Seppala et al. [37]	2018	Systematic review and meta-analysis	248	Antipsychotics Antidepressants Benzodiazepines	Significantly high risk of falls in patients > 60 years of age
Takkouche et al. [38]	2007	Systematic review and meta-analysis	98	Psychotropics	Higher risk of fractures in elderly patients
Treves et al. [39]	2018	systematic review and meta-analysis	14	Sedative hypnotics	Substantial increase in the risk of falls and fractures
Oderda et al. [36]	2012	Meta-analysis	19	Antidepressants Antipsychotics	High association of hip fractures in patients > 65 years of age
Lee et al. [35]	2017	Systematic review and meta-analysis	19	Antipsychotics	Significantly higher risk of lower limb fractures in elderly population

Table 3: Studies describing the association of psychotropics and fractures.

and lower socioeconomic status. Interventions targeting bone health and anticipating risks of falls and fractures in these patients need to be developed and implemented in routine practice. The treating orthopaedic clinicians and hospital staff should be aware of high-risk patients to ensure appropriate surgical planning and coordination with physical therapists, mental health specialists, and social workers to maximize patient outcomes and minimise the utilisation of resources. Strategies should be in place for early identification of psychiatric and drug-related issues on admission and to mobilise the relevant resources and psychosocial support to facilitate discharge and recovery pathway.

Competing Interests

None.

Contributorship

Both authors confirm that we had:

Substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; AND

Drafting the work and revising it critically for important intellectual content; AND

Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding Statement

This article received did not receive any grant from any funding agency, commercial or not-for-profit sectors.

Ethical Approval Information

This article did not meet the criteria for obtaining an ethics committee or institutional review board approval as it does not reveal any identifiable personal, sensitive or confidential information of the participants of the included studies.

Data Sharing Statement

Both the authors confirm that data file will be available to share on a reasonable request.

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