



BIPOLAR DISORDERS: REVIEW OF EMERGING PHARMACEUTICAL TREATMENT AND USE OF MOBILE TECHNOLOGY TO IMPROVE ADHERENCE AMONG BD PATIENTS

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ABSTRACT

Mood disorders are of public health concern and non-adherence to medication seems to be a major issue in mood disorders such as bipolar. A plethora of pharmacological treatment intervention exist for mood disorder but their universal effectiveness have not been achieved especially because some of the treatments are associated with uncomfortable side effects which affect treatment, particularly medication adherence. A review of the emerging or investigational pharmaceutical treatment for bipolar disorder was conducted. The pharmacokinetic and pharmacodynamic of first generation long-acting injectable antipsychotic such as Flupentixole Decanoate was reviewed. The paper reviewed several researches and discourses on the use of mobile technology as a viable option for improving medication adherence among patients with mood disorders. The Benefits of use of mobile technology for medication adherence in mood disorders was discussed and the challenges with the use of mobile technology for medication adherence in mood disorders were also reviewed. Consequently, the gaps yet to be understood with the use of mobile technology for medications adherence in mood disorders was identified. The review concludes that long acting injectables has the potential to be used for treating all stages of depression and agitations which mainly characterize bipolar experiences. It is further concluded that there are prospects with the use of mobile technology in the improvement of medication adherence among mood disorder patients.

Key words: Mobile Technology, Mood disorder, Adherence, medication

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INTRODUCTION

Bipolar mood disorder is characterized by an experience of depression and mania or hypomania. Bipolar is a common and severe psychiatric disorder with high rates of readmission, relapse and nonadherence to medication as a major complication (Fontaine, 2008). Bipolar disorder causes mood swings and has been reported to be responsible for a high rate of premature mortality (Biazus et al, 2023). The onset of bipolar disorder can be recognized by a recurrent mood fluctuations and energy states which becomes chronic over time. The onset age is between 15 and 25 years with depression frequently manifested in the initial presentation stage (Nierenberg et al, 2023). Research indicates that more than 1% of the world's population of people from different ethnic origin, nationality or socioeconomic status is affected by bipolar disorders (Grande, Berk, Birmaher & Vieta, 2016). Bipolar disorder is a mental health condition that is characterized by an alternation between manic episodes and depression. Manic episodes in bipolar disorder are accompanied with symptoms like elevated mood, increased energy, psychotic symptoms and more while the depressive episodes are characterized by decreased energy, sadness, suicidal

thoughts fatigue and other cognitive disabilities (Khanra et al, 2013).

Bipolar disorder has been seen as leading cause of disability among young people which also causes cognitive and functional impairment among the affected persons. It has also been linked to high to an increased mortality rates especially death through suicide (Grande, Berk, Birmaher & Vieta, 2016). Grande et al (2016) further noted that in clinical practice, there is a difficulty in accurate diagnosis of bipolar disorder because its onset is characterized by depressive episodes which resemble those of unipolar depression. Meanwhile, mania or hypomania are also present in bipolar just as depression. The episodes of mania and hypomania cause distinct changes in mood and behaviour of bipolar patients and occur at discrete time periods (Nierenberg et al, 2023).

Depressive episodes or symptoms account for about 75% of all symptomatic time in bipolar disorder and as Nierenberg et al (2023) opined, diagnosing and treating bipolar early enough leads to a favorable prognosis. Meanwhile, Goes (2023) research suggest that early diagnosis of bipolar disorder is challenging because misdiagnosis are frequent which delays early intervention and increase the risk of

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iatrogenic harm. Long term treatments of bipolar disorders are achieved through the use of mood stabilizers such as lithium, valproate, and lamotrigine. Other antipsychotic agents, such as quetiapine, aripiprazole, asenapine, lurasidone, and cariprazine are also recommended for bipolar treatment, but some are known to be associated with weight gain (Nierenberg et al, 2023). While several medications abound for the treatment of bipolar disorder, predicting the medication that will be most likely tolerable or effective is yet to be possible (Goes, 2023). This is an indication that cutting edge and expository research in bipolar disorder pharmacology is yet to have a breakthrough. Classified as among the leading cause of disability in the world (Garey et al, 2014), bipolar disorder, like other psychiatric disorders has suffered from dearth in new pharmacological intervention (Harrison et al, 2016).

Emerging or investigational pharmaceutical treatment for bipolar disorder

Historically, pharmaceutical treatments for bipolar disorder are focused on mood stabilization and reduction of psychotic episodes of depression. Long-acting injectable antipsychotics (LAIs) have been identified as an emerging potential efficacious therapeutic option for the

treatment of bipolar disorder as shown by real-world data and clinical trials (Bartoli et al, 2023).

The pharmacokinetic and pharmacodynamic of Long-acting injectable antipsychotics (LAIs)

The European Medicine Agency (EMA) and the United States Food and Drug Administration (FDA) approved the Long-acting injectable antipsychotics as a therapeutic option for the improvement of adherence in bipolar disorder (Bartoli et al, 2023). First generation long-acting injectable antipsychotic such as Flupentixole Decanoate and theoxanthene antipsychotic has been seen as having a pronounced antidepressant and anxiolytic effect that is good for treating all times of stages of depression (Pödlinger and Sieberns, 1983).

Flupentixole Decanoate works through intramuscular injection. The drug's initial and maintenance dose is 20-40mg in every 2-3 weeks but it is also reported that doses of Flupentixole Decanoate close to the recommended dose are still effective (Bailey and Taylor, 2019). Research has long hypothesised that Flupentixole Decanoate could become an alternative to lithium in the treatment of recurrent manic and depressive illness all of which

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characterize bipolar disorder (Ahlfors et al, 1981). There has been a manifestation of the prediction as Flupentixole Decanoate has been demonstrated to produce long lasting effect as well as being a well-tolerated pharmacological choice for people with bipolar disorder (Bartoli et al, 2023).

Long-acting injectable antipsychotics as Flupentixole Decanoate are classified as depot antipsychotics and they exhibit flip flop kinetics where absorption rate determines the time at steady state, while the elimination rate determine the concentration at steady rate (Jann et al, 2019). This creates a clinical impression suggesting that Flupentixole Decanoate produce a sustainable effect in reducing relapse and non-adherence observed with other treatment of bipolar disorder. Drug Bank Online (2022) claim that flupentixole act by producing mild sedative actions as well as being an antipsychotic anxiolytic.

Flupentixole Decanoate has a capacity to interact with major binding sites of dopamine and serotonin due to its broad profile which are very relevant to the neurobiology of depression. It also exerts weak adrenergic and anticholinergic effects Drug Bank Online report (2022) have shown. Other studies (Dong et al,

2019), revealed that flupentixole produced an inhibition of P13K/AKT pathways as well as inhibited survival of lungs cancer cell both in vivo and in vitro.

Limitations identified from Lithium treatment of bipolar disorder that LAIs address

The use of lithium in treatment of bipolar disorder was seen as a gold standard because of its effect in managing manic and depressive episodes in BD as is referred to as first-line mood stabilizer (Girardi et al, 2016). Meanwhile, there are some identified difficulties in the prescription of lithium. For instance, lithium presents a potential long term effect on thyroid and renal functioning (Boyce et al, 2018). These perceived limitations have limited the use of lithium for bipolar disorder because alternative treatments strategies are required, again due to the fact that blood levels need to be monitored regularly when lithium is used for bipolar treatment (Boyce et al, 2018).

In an attempt to achieve long term treatment for bipolar disorder, more recent long-acting injectable which fall under the second-generation antipsychotics (SGs) were introduced as they were more effective for maintenance (Boyce et al, 2018). The reason why long-acting

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injectable preparations are preferred to lithium is because they act more on maintaining the recovery and prevention of reoccurrence of the disorder. Long-acting injectable antipsychotics have the benefit of stabilizing blood levels which was lacking in the lithium treatment for BD and they have an improved pharmacokinetics when compared to lithium (Spanarello and Ferla, 2014).

The new treatment of bipolar disorder with flupenthixol decanoate has greater potential for preventing relapse. Owing to this, in 2009 the USA FDA approved some long-acting injectable so serve as a monotherapy and as an adjunct therapy to lithium for maintenance treatment of BD (Kishi et al, 2016). Likewise, it was observed that bipolar disorder patients who switched to long-acting injectable displayed objective clinical efficacy which exceeded those of oral atypical antipsychotics such lithium as clinical studies revealed (Chou et al, 2015).

Studies by Pacchiarotti et al (2019) show that long-acting injectable such as flupenthixole decanoate are more efficacious for depression and mania which are major symptoms in bipolar disorder. Other researches by Eker et al (2015) observed that treatment of bipolar disorder using flupenthixole decanoate reduced

hospitalization during when compared to when patients were treated with lithium. The various side effects associated with lithium treatment for bipolar disorder are some of the deficiencies observed which long-acting injectable address in bipolar treatment.

Challenges presented by Long-acting Injectable

There are some perceived limitations associated with the use of long-acting injectable like flupenthixol decanoate. There is a potential for patients to have a feeling that they have lost their autonomy and again, there is stigmatization associated with having regular injections (Boyce et al, 2018). Other challenges with the use of flupenthixol decanoate medication for bipolar disorder exist as studies have shown that the medication is not suitable for bipolar patients who present agitated depression or those with suicide ideation (Pöldinger and Sieberns 2008).

Pöldinger and Sieberns (2008) further observed that there could be extrapyramidal movement disorder when using flupenthixol decanoate for treating bipolar disorder which can be seen as a disadvantage of the medication. Meanwhile, the scholars found that the

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disorder is rarely encountered with the correct dose given.

Stage of development of long-acting injectable

Long-acting injectable treatment varies relatively across the world. As with other depot formulation treatment, flupenthixole decanoate is still undergoing development as clinical trials of the medication efficacies are ongoing. Flupenthixole decanoate a long-acting injectable was developed around 1970 (Bailey and Taylor, 2019). Studies by Velligan et al (2010) indicate that the prescription rates are higher in some countries like France and the United Kingdom when juxtaposed with other countries in Europe. In Africa, research shows a 13.9% acceptance and use of flupenthixol depot injectable (Arute et al, 2015).

The efficacy of flupenthixol decanoate in the treatment of bipolar disorder has been established in several researches. The long-acting injectable observed to significantly improve the functionality of patients with bipolar disorder as the number of mood episodes they experienced was decreased after being exposed to the medication (Eker et al, 2015). There have been earlier suggestions to show the efficacy of flupenthixol decanoate as a second

generation antipsychotic medication. Thus, findings from Bond et al (2007) suggest that the medication reduce the frequency of manic and depressive episodes and are well tolerated by the bipolar patients especially in maintenance treatment.

Flupenthixole decanoate cost an average \$7.7384 for 20mg/ML 100mg/mL given through injection. The recommended dose is 20mg to 40mg Intra Muscular (IM) every 2 to 3 weeks (National Library of Medicine, 2017). The price is moderate because studies have compared the cost effectiveness of the LAIs when compared to patients' previous treatment of bipolar with oral medications. Thus, as research by Mahlich et al (2020) have shown, in Germany, patients had high medication cost post switching to long acting injectable such that treatment cost went from €383 to €799. This also indicates that hospitalizations days reduced with LAI treatment.

Although further systematic studies are needed to fully assess the overall efficacy of long-acting injectable as flupenthixol decanoate, research evidence suggests that this SGA does not increase the burden of the depression associated with bipolar

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disorder as it is efficacious in maintenance treatment of the disorder (Bond et al, 2007).

Antidepressants are not recommended as monotherapy in bipolar disorder but alongside those of mania and hypomania. Nierenberg et al (2023) noted that the prevalence rates of metabolic syndrome is (37%), obesity (21%), cigarette smoking (45%), and type 2 diabetes (14%) are higher among people with bipolar disorder, which contributes to high risk of early mortality. This is further orchestrated by nonadherence to psychotropic medication by bipolar patients which has become a significant problem in the treatment of bipolar disorder (Perlick et al, 2004).

It is further known that approximately 15% to 20% of people with bipolar disorder die by suicide and more than 50% of bipolar patients are non-adherent to treatment (Nierenberg et al, 2023). Non-adherence to medication in bipolar disorder as other studies have shown happen in 20-60% of patients with BD with severe negative outcomes (Lewin et al, 2015). Some of the negative effects are summarized as relapse, hospitalization, suicide, incarceration and high cost of healthcare (Lewin et al, 2015). Mediating these negative outcomes gave rise to the consideration of mobile technology for improvement of medication

adherence in mood disorders and particularly bipolar disorder.

Benefits of use of mobile technology for medication adherence in mood disorders

Some factors that predict non medication adherence in mood disorder patients range from comorbidity with substance abuse, poor therapeutic alliance, younger age, side effects related to treatment and the specific features of the disease (Pompili, 2014). Other factors that cause non medication adherence in mood disorder patients include the patients' beliefs, the severity of the illness and poor insight as finding from a review by Pompili et al (2014) has shown. Owing to the social, clinical and economic impacts that nonadherence to medication has on mood disorder patients, developing new interventions that are able to improve adherence becomes imperative.

The use of mobile technology to improve medication adherence among patients with mood disorders is gaining impetus as an effective intervention approach. For instance a pilot study by Wenze, Arney and Miller (2014) indicates that mobile technology helped the patients to identify and evaluate the precursors to their nonadherence which could not be achieved through face to face intervention. Thus, mobile technology helps patients to identify

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the causes of their nonadherence both on a momentary and on an ongoing basis. Economically, mobile technology is cost effective because it reduces the cost of transportation and other logistics required to achieve a face to face treatment approach (Wenze et al, 2014). Mobile technology can also assist mood disorder patients self-manage their mood symptoms (Depp et al, 2015).

Other studies has shown that there is significant improvement in mobile technology use for medication adherence for mood disorder with text messaging appearing promising for adherence to medication in a variety of mental health population (Watson, 2017). Therefore, available research evidence shows that mobile technology is ubiquitous, easy to use, saves cost, and helps to communicate with patients outside of their in-patients visits (Rootes-Murdy et al, 2018). Wiecek et al (2020) in a study concluded that mobile technology interventions for medication adherence which uses dosage reminders, gamification, incentives in mood disorders appears to be an effective promising strategy which will impact adherence to medications positively in real practice.

Challenges with the use of mobile technology for medication adherence in mood disorders

Just as with other intervention approaches, mobile technology for improving medication adherence in mood disorder is faced with challenges. It is therefore not possible to address and tackle all the risk factors in nonadherence through the use of mobile technology intervention strategy (Wenze et al, 2014). Challenges or limitations are sometimes related to high acquisition and subscription cost, difficulties handling new technology and software speed among other technical issues (Watson et al, 2017).

Although Rootes-Murdy et al (2018) study found that all the studies reviewed indicated that mobile technology does improve medication adherence in mood disorder patients, Wenze et al (2014) observed some limitations with the use of mobile technology strategy such as the size of screen, software processing speed, participant burden, and maximum character display on device and complexity tradeoffs. Other challenges lies with how to improve accessing and managing consistent mobile technology use and individual preferences when using mobile technology based intervention (Watson et al, 2020). Thus,

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mobile technology interventions such as text messaging may present a challenge of quantification with determining the patient that will benefit the most with text messaging interventions (Watson et al, 2020).

Gaps yet to be understood with the use of mobile technology for medications adherence in mood disorders

While mobile technology intervention promises to improve medication adherence in mood disorder and benefits the field, scholars are yet to address issues relating to intentional nonadherence. Intentional nonadherence suggest an affirmative decision patients take to forgo medications prescribed to them (Basit, Mathews, & Kunik, 2020). Thus, mobile technology will work for unintentional nonadherence where the patient is either forgetful or careless. Other reasons for unintentional nonadherence include problems with using the treatment, poor recall, inability to pay for the treatment, difficulties in understanding the medication instructions among other factors (Nunes et al, 2009). Nunes et al, (2009) argued that medication nonadherence in bipolar should be seen as the patients' problems but as a fundamental limitation in the delivery of healthcare to patients needing mental health services.

Intentional nonadherence will pose a challenge to the growing body of literature promoting use of mobile technology for medication adherence in mood disorder and thus presents a knowledge gap yet to be understood. This is because the knowledge of patient's perspectives and their reasons for making the affirmative decisions of non-adherence has not been properly explored using empirical studies. Although attempts to understand why patients with serious mental illness do not adhere to medications has identified factors such as negative attitude to medication, substance abuse, medication side effects and cognitive impairment as major causes of nonadherence (Velligan et al, 2017), patients' specific poor adherence drivers are fully unknown, which are of important clinical implications.

Location is among some of impediments to the use of mobile technology intervention in medication adherence among bipolar patients. Mobile technology can be used for improving medication adherence in developed communities and population with regular network and internet. For instance Agyapong et al (2016) research found text messaging very effective in closing treatment gap for patients with mental health issues in Alberta Canada and

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suggested that it can be so elsewhere. This is however not totally correct because in some developing countries in Africa and communities where there are poor network connections, mood disorder patients who unintentionally do not adhere to medication due to forgetfulness may not get the reminder on time due to network failure. Likewise, the uneducated class of patients who lack the literacy and capacity to operate the mobile phones will not benefit from the use of mobile technology to improve medication adherence. A randomized control trial research indicating how effective this approach is in varying contexts is needed.

Conclusion

Long acting injectables have long become a new form of treatment for bipolar disorder

and they have been proven more effective in managing non-adherence to medication when compared to previous forms of treatment such as the popular lithium. Long acting injectables such as Flupenthixole decanoate has the potential to be used for treating all stages of depression and agitations which mainly characterize experience with bipolar. The efficacy of the use of long acting injectable as those of flupenthixole decanoate is found in its ability to prolong duration of action. Trials studies further support the hypothesis that flupenthixole decanoate could serve as alternative to lithium in BD treatment. Likewise, medication adherence can be improved with the use of mobile technology notwithstanding the knowledge gap in addressing intentional nonadherence with mobile technology interventions.

DECLARATIONS:

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