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Options when anti-depressants cannot be used in conventional ways. Clinical case and review of literature

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ABSTRACT

Psychiatrists are often faced with the challenge of treating patients who cannot take pills or refuse to take pills. While there are many antipsychotics available in different formulations, the availability of antidepressants in alternative formulations is quite limited. The aim of this paper is to discuss various antidepressant options and management strategies practically available for psychiatrists in such situations, especially in the United States (US) and in many other countries of the world. Although there have been review articles on this topic, most of them have focused on formulations that are still in the experimental stage or drugs available in different parts of the world, especially Europe. There will also be brief discussion of formulations which have been used in clinical studies that are not yet licensed for commercial use as these formulations may widen therapeutic avenues for depression in future.

1. Introduction

Depression is a common mental illness that robs patients of simple joys in life – independence, precious time, and meaningful experiences. It is a devastating illness which requires prompt diagnosis and treatment. Depression is often found co-morbid with various medical illnesses such as arthritis, asthma, cancer, cardiovascular disease, diabetes, hypertension, chronic respiratory disorders, and a variety of chronic pain conditions adding tremendously to the morbidity burden [1].

Oral administration via tablet or capsule is the predominant route of delivery of antidepressants. However, there are times these medications cannot be given orally. Certain contraindications and disadvantages to oral administration are that pills may (1) be inappropriate for some patients like those who must be given nothing by mouth, (2) irritate gastric mucosa and cause nausea and vomiting, (3) be aspirated by seriously ill or uncooperative patients, (4) be destroyed by digestive enzymes, (5) have an objectionable taste or may be difficult to swallow, and (6) harm or discolor the teeth [2]. In scenarios such as these, there is a need for medications that can be given by alternative routes.

The need for finding commercially available antidepressants that could be used by a route other than oral presented itself after we were consulted regarding the following case.

Mr. Z is a 38 year-old male with stage I diffuse large B cell lymphoma encasing his small bowel. He received several rounds of the appropriate chemotherapy regimen and was admitted three months prior for small bowel perforation, which resulted in jejunal resection and primary anastomosis. During the same admission, he developed duodenal perforation and intra-abdominal fluid collection, which required placement of a percutaneous drain. These series of events rendered oral intake no longer feasible. Mr. Z was put on total parenteral nutrition and could not receive any of his medications by mouth.

A psychiatry consult was placed to evaluate Mr. Z's depressed mood and provide treatment recommendations considering his inability to take oral medication. Upon evaluation, he reported two weeks of depressed mood, changes in sleep, guilt, decreased energy, trouble concentrating, psychomotor slowing, and suicidal ideation. He had no history of personal or family psychiatric illness and his substance abuse history was not significant. A diagnosis of depression due to multiple medical comorbidities was made, and now the consultation liaison (CL) psychiatry team was faced with the dilemma of finding a suitable treatment option for Mr. Z.

The decision was made to start Mr. Z on Mirtazapine (Remeron) Sol Tab 15 mg, an orally disintegrating tablet, every night and monitor for improvement in mood and suicidal ideation. This choice was our first intervention as mirtazapine is available in a formulation that is readily *absorbed* by the mucosal surfaces in the mouth. Intramuscular (IM) or intravenous (IV) antidepressant formulations are not readily available

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in the United States, therefore, if no improvement was made after few weeks, reassessment and treatment with intradermal selegiline, intravenous ketamine administration, or ECT was considered as a possible next step. On follow-up, Mr. Z revealed that he was doing much better, though still mildly depressed, and that his suicidal thoughts were now markedly diminished.

2. Discussion

Oral route is the most commonly used mode of administration for prescription antidepressants; however, the patient in this case needed an antidepressant in alternative formulation. When confronted with such a situation psychiatrists are often challenged as there is a dearth of options. Here we will briefly describe some practical options that can be tried in such situations. Though few, there are options available when antidepressants cannot be used in conventional ways.

Search Strategy and Selection Criteria: We searched electronic databases including MEDLINE, EMBASE, Scopus, Google Scholar, and Science Direct to collect literature for the review. References for our review were collected from a period of January 1985 to present. We used scholarly papers using the keywords “alternative routes”, “non-conventional routes”, ‘‘intravenous”, “transdermal”, “oral disintegrating tablets”, “intramuscular”, “intranasal”, “rectal suppositories”, ‘‘selective serotonin reuptake inhibitors”, “tricyclic”, “citalopram”, “clomipramine”, “amitriptyline”, “antidepressants”. We excluded articles that reported use of antidepressants in psychiatric conditions other than depression (e.g. anxiety, obsessive compulsive disorder) and non-psychiatric conditions (e.g., pain), articles that examined the effects of medications in animal models, and articles published in languages other than English.

Upon extensive search we found that IV formulations were still experimental and not readily available commercially in many parts of the world. As a result, we were unable to treat this patient with an IM or IV medication. The alternatives available to us were mirtazapine, selegiline and olanzapine (as an augmenting agent) orally disintegrating tablets (ODTs), selegiline transdermal system (STS), and ketamine (off-label drug).

Mirtazapine (Remeron) and selegiline (Zelapar) are commercially available in ODT formulations. Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). Its mechanism of action appears to be related to antagonizing the adrenergic α_2-autoreceptors and α_2-heteroreceptors and by blocking 5-HT2 and 5-HT3 receptors, thus increasing the release of norepinephrine and 5-HT1A – mediated serotonergic transmission [3]. Selegiline is an irreversible monoamine oxidase (MAO) inhibitor which potentiates the activity of serotonin, noradrenaline (norepinephrine) and dopamine [4]. Apart from antidepressants olanzapine, a second generation antipsychotic, available in ODT formulation may be used as monotherapy in bipolar depression [5] and as augmentation therapy in unipolar depression [6].

Oral disintegrating tablets are variously known as fast disintegrating tablets (FDTs), fast melting tablets, orodispersible tablets, fast dissolving/dispersing tablets or melt in mouth tablets [7]. ODTs primarily get absorbed into the body by several pathways. Many are absorbed by the buccal route [8]. They are usually taken without water and once in the buccal cavity they disintegrate rapidly in saliva, usually in a matter of seconds. ODTs may be significantly better than conventional dosage forms in terms of drug dissolution, absorption, onset of clinical effect and drug bioavailability [9,10]. In a study done by Shoukri et al it was found that the rate of absorption of nimesulide from ODT was faster than that from the reference tablet. ODT had a significantly higher ($p = 0.012$) peak plasma concentration, and shortened time to C(max) (the maximum concentration) by 1 h ($p = 0.029$). The extent of absorption expressed by area under the curve (AUC) was 62% larger when compared to the commercially available tablet [11]. In another study that examined the pharmacokinetics, it was found that the administration of selegiline using an ODT improved both the AUC (area under the concentration time curve) and C(max) by approximately five-fold compared with a conventional dosage form [10]. The ideal characteristics of a drug for in vivo dissolution from an ODT include 1) palatable and not bitter in taste; 2) small to moderate molecular weight; 3) good stability in water and saliva; 4) partially non-ionized in the oral cavity pH; 5) ability to diffuse and partition into the epithelium of the upper gastrointestinal tract; and 6) ability to permeate oral mucosal tissue [12].

There are some remarkable features of ODTs that make them better than conventional tablets: (1) They are easy to administer to patients who refuse to swallow a tablet or have difficulty in swallowing, such as pediatric, geriatric and psychiatric patients. (2) More accurate dosing can be used in comparison to liquid formulations which may be another option when patients have difficulty swallowing. (3) The dissolution and absorption of the drug is very fast which may produce rapid onset of action. (4) The absorption from the buccal mucosa, pharynx and esophagus may result in improved bioavailability. As a result reduced dosage may be needed, thus decreasing unwanted side-effects [7]. There are a couple of caveats that should be kept in mind while prescribing ODTs. They must be used with caution in patients with Phenylketonuria as many ODTs contain phenylalanine [13]. Also with medications like Mirtazapine, lesser doses may be required in hepatic and renal impairment, when used in ODT formulation as ODT could lead to higher drug levels [14].

The other option that was considered in this case was selegiline transdermal system (Emsam). This is the only US Food and Drug Administration (FDA) approved transdermal delivery formulation for major depressive disorder. By this route, selegiline gets directly absorbed into the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism. The patch is applied once daily for the treatment of major depressive disorder [15]. It comes in three different doses and patch sizes: 6 mg/24 h patch, 9 mg/24 h patch, and 12 mg/24 h patch. As the transdermal delivery system avoids gastrointestinal tract exposure it minimizes food-drug interaction risks associated with MAO inhibition in the gut and thereby enhances the safety of the selegiline given at standard doses. Thus, if an alternate route is needed then the selegiline transdermal system provides psychiatrists with a potentially helpful treatment option, which is FDA approved and commercially available [8,15].

The CL team also considered ketamine as an option as it is readily available and providing an IV infusion would have been easily accomplished. Ketamine, an anesthetic agent, though not FDA approved for depression, has shown a lot of promise and potential in treatment of depression. It can be given to the patient as an infusion (IV) or IM injection. Ketamine has effects on the glutamate neurotransmission system. Glutamate has three ionotropic receptors: N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate. The primary mechanism of action of ketamine is by blocking the NMDA receptor at the phencyclidine (PCP) site within the ionotropic channel. AMPA receptors are frequently co-expressed with NMDA receptors, where they act in concert causing alteration in glutamate levels and synaptic plasticity [16] which is a proposed mechanism of how it helps in the treatment of depression [17]. It has been hypothesized that alterations in the regulation of glutamatergic neurotransmission contribute to the pathophysiology of major depressive disorder, as well as to the mechanism of existing antidepressants [16].

There have been several studies that have supported ketamine use as an antidepressant. The first double-blind, placebo-controlled (crossover) study was described by Berman et al. (2000), which showed that an intravenous ketamine infusion (0.5 mg/kg) resulted in significant, and rapid, but short-lived, antidepressant effects in seven patients with major depression [18]. This was followed by the study of Zarate et al. in 2006. He described the first randomized, double-blind, placebo-controlled (crossover) study of ketamine in 18 patients who had treatment-refractory major depressive disorder. Ketamine was administered as an intravenous infusion in normal saline at a dose of 0.5 mg/kg across a

40-minute period; the placebo in this study comprised normal saline without ketamine or any other medication. Patients receiving ketamine reported significant antidepressant benefit within 110 min of the ketamine infusion. One day later, the response and remission rates to ketamine were 71% and 29%, respectively. However, only six patients (35%) maintained response for one week. In contrast, the response rate to saline infusion was 0% after both one day and one week [17,19]. Since then, several studies and case reports have shown successful use of ketamine in alleviating depression. Ketamine is also reported to have anti-suicidal properties. Most studies have demonstrated that ketamine is associated with rapid onset of anti-depressant and anti-suicidal effects in patients with major depression. It is also effective in treatment-refractory depression. It is effective when administered at a dose of 0.5 mg/kg in normal saline as infusion. Due to rapid onset of action, the anti-depressant action is seen to develop within 1–2 hours of the infusion, peaks 1–2 days later, and persists for up to a week [17].

There are certain problems encountered with ketamine use. It is associated with adverse effects like confusion, dizziness, euphoria, perceptual disturbances, and increased blood pressure; these are usually short-lived and last for not more than 1–2 hours. To have sustained effect, repeated infusion of ketamine is warranted, as it is associated with maintained antidepressant effects for up to nearly two weeks; and discontinuation of treatment is associated with relapse after an average of nearly three weeks [20]. Ketamine's use in psychiatric illnesses is also limited by the fact that it has significant reinforcing and toxic effects. It has abuse potential that can cause severe harm. Its long-term use may also disrupt learning and memory processing [21].

Apart from the pharmacological options, there are other biological therapies available like Electroconvulsive treatment (ECT), Deep Brain Stimulation (DBS), Transcranial Magnetic Stimulation (TMS) and Vagal Nerve Stimulation (VNS) which can be used in such patients. In meta-analysis done by Pagnin et al. (2004) it was found that ECT is a valid therapeutic tool in the treatment of depression, including severe and resistant forms [22]. However, ECT is not without side-effects, like cognitive deficits and memory loss which may cause a patient to refuse treatment preemptively [20]. ECT use also has some practical limitations. The ECT machine and the associated equipment may not be available in all settings. Many psychiatrists are not experienced with the technique and ECT administration may be expensive. At times, the psychiatrist is dependent on the requirement of an anesthesiologist, technician, family member, or a person to escort the patient, all of which may further increase the overall cost of treatment [23].

TMS is another brain stimulation technique which has been approved by the FDA for adults with depression who have failed to respond to antidepressants. It is safe and well tolerated. Considering its favorable side effect profile, it may also be indicated for patients who are intolerant of medications or cannot take antidepressants orally [24].

VNS and DBS are other forms of brain stimulation methods involving invasive techniques as they require surgical approach and are also expensive. These forms of treatments are therefore reserved for patients with extremely high level of treatment-resistance, usually after the patient has failed a course of ECT [24].

ECT, TMS, VNS, DBS are some options which may not always be practical or feasible. Pharmacotherapy is the initial treatment of choice and other somatic therapies like ECT, TMS etc. are usually tried in severe cases or failed response to antidepressants [25].

Psychotherapy could also be considered for the management of depression in patients where medications cannot be utilized for various reasons. Various types of psychotherapies include cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), psychodynamic psychotherapy, problem solving therapy, marital or family therapy and group therapy. Most research has focused on individual psychotherapy in the outpatient setting, but it is expected given adequate time psychotherapy might be beneficial for inpatients as well. CBT, IPT, and behavioral psychotherapies (e.g., behavioral activation) have been found to be the most effective in treating major depressive disorder [25]. Psychotherapy is generally found to have more prolonged effects than pharmacotherapy after cessation of active treatment [26–28].

The effectiveness of psychotherapy will vary with the skill and training of the therapist, and it is not free of adverse effects. For instance, secondary feelings of anxiety generated by psychotherapy may compound the primary illness, and some patients may get frustrated by the time commitment involved. The treating psychiatrist should dynamically adjust goals of and expectations from psychotherapy, and make changes to medication regimen if 4–8 weeks have elapsed without significant improvement [25].

2.1. Drug formulations still in research stages

In the following paragraphs we discuss some antidepressant formulations that have been tried in studies, but are not yet commercially available and also some antidepressants that have potential to be developed in different formulations.

2.2. Intravenous antidepressants

IV antidepressants are not commercially available in the US and Canada. Although there are some formulations which have been developed by pharmaceutical firms in Europe, many such products do not have formal licenses. They may be very difficult to obtain, being available only through pharmaceutical importers or from special manufactures [6]. It is thought that IV antidepressants would have faster onset of action and greater efficacy. Studies have been conducted with IV formulations of citalopram [29–31] amitriptyline [32], mirtazapine [33,34], clomipramine for obsessive-compulsive disorder [35–37] and maprotiline [38,39]. These studies showed some trends, but overall there were no statistically significant results favoring IV formulations over oral in terms of efficacy, tolerability, or onset of action. Citalopram is the only antidepressant available in IV formulation that has consistently produced favorable results and is reported to have an excellent tolerability profile and equal efficacy with its oral counterpart. It is also reported to be more efficacious in more severely ill patients. [40]

2.3. Intramuscular

Psychotropic medications delivered by IM route are currently used for two purposes: to provide rapid tranquilization in an emergency setting and as depot antipsychotics [41]. The salient features of IM route are fast absorption, avoidance of first-pass metabolism, and ensured compliance. However, there are a few short comings such as bioavailability is often less than 100% because of drug retention and metabolism by local tissues, repeated injections of some drugs may cause local irritation or abscesses, and cautionary use in cachectic patients and those with poor muscle perfusion [42]. Although there are many antipsychotics that can be used by this route, we still do not have many antidepressant formulations that can be given intramuscularly. IM amitriptyline (Elavil) can be used in a concentration of 10 mg/ml, which requires a high-volume injection. This discourages its use as IM injection [6]. IM ketamine appears to be a promising agent. There is evidence of ketamine 0.5 mg/kg IM injection rapidly alleviating depressive symptoms and suicidal ideation [43].

2.4. Inhalational

Inhalation route could be a potentially beneficial route for systemically acting medication owing to the large surface area of the lungs and the good relative permeability of vasculature. Smaller, lipophilic compounds are absorbed rapidly and result in higher bioavailability. In general, a dose of approximately 20 mg may be administered via inhalation. Ideal properties of drugs administered via this route include a molecular weight of less than 10,000 g/mol, a log P of −1 to 2 (log P is

the degree of lipophilicity needed to promote adequate drug absorption), and a pKa of 4–9 (pKa is the acid dissociation constant that would most favorably affect the drug ionization at the site of drug delivery). Tranylcypromine and phenelzine are some medications that fulfill these properties and thus have a potential to be used in the form of inhalational administration [8].

2.5. Intranasal

Absorption through the nasal passages bypasses the gut and also allows transport of drugs into the central nervous system via the olfactory and trigeminal nerve pathways. Intranasal administration can be used to deliver doses of up to approximately 20 mg. Ideal drug characteristics for administration via this route include a molecular weight less than 1000 g/mol, a log P of 1–4, and pKa of 4–9.6. There are several antidepressants that could potentially be developed for use by this route owing to their molecular properties like citalopram, escitalopram, paroxetine, venlafaxine, desvenlafaxine, doxepine and mirtazapine [8]. Ketamine is also effective when used via intranasal route. Lapidus et al. conducted a randomized, double-blind, placebo-controlled, crossover trial involving 20 patients with major depression who were randomly assigned to intranasal ketamine (dose of 50 mg) versus placebo (saline). It was found that patients in ketamine group showed significant improvement in depressive symptoms at 24 hours compared to placebo. Intranasal ketamine was well tolerated with minimal adverse effects [44].

2.6. Sublingual

In this route, the drug is placed in between the tongue and lower surface of mouth. The sublingual site has rich supply of capillaries and high permeability thus promoting rapid absorption and also bypassing the first-pass metabolism. This may be an effective route, especially for non-ionized, highly lipid-soluble medications [41]. A case report describes the use of sublingual fluoxetine in two patients unable to be treated with oral antidepressant therapy because of gastrointestinal complications. Fluoxetine liquid (20 mg/5 mL) was administered sublingually via dropper by a trained staff member. It was initiated at 10 mg daily and escalated up to 20 mg daily in both patients. The serum levels of fluoxetine and its major metabolite norfluoxetine were within a therapeutic range by week four of treatment, and both patients were maintained on the sublingually administered antidepressant until they were ready to switch to oral formulation. Both patients had improvement in depressive symptoms with sublingual fluoxetine [45]. Other antidepressants available commercially in liquid formulations include Escitalopram (Lexapro) 5 mg/5 mL, Doxepin (Sinequan) 10 mg/mL, Imipramine (Tofranil) 10 mg/5 mL, Nortriptyline (Aventyl, Pamelor) 10 mg/5 mL, Paroxetine (Paxil) 10 mg/5 mL [46]. Lithium, also available in liquid formulation, may be used as monotherapy in bipolar depression [47] and as augmentation therapy in unipolar depression [6]. However there is a dearth of studies using these formulations via sublingual route.

2.7. Rectal

Rectal route of administration has less predictable absorption as it is dependent on various factors such as, surface area over which the drug is absorbed, the rate of drug dissolution, the amount of non-ionized drug at the site of absorption, and the retention time of the medication. However, rectal drug administration can be advantageous since it results in reduced first-pass metabolism as approximately half of the drug dose will bypass the liver [8]. Currently there is no antidepressant that is commercially available as a rectal preparation, but there have been case reports that have documented some success with the use of trazodone suppositories [48], amitriptyline suppositories [49], doxepin capsules inserted with suppository base [50] and fluoxetine suppositories [41,51].

3. Factors contributing to poor adherence

If a patient refuses to take medications one must explore the possible reasons behind it. There could be multiple reasons that leading refusal of medications or poor adherence. Factors leading to poor adherence may be broadly categorized as 1) patient related; 2) clinician related; 3) illness related; and 4) medication related.

Some of the patient factors include concerns about the side-effects, few perceived benefits, stigma of taking medication, adjustment to suit daily routine, concerns about cost, concerns about availability, and concerns about dependency. Clinicians may also be responsible for poor adherence if they have a poor doctor-patient relationship, fail to express empathy, provide suboptimal explanations, or communicate poorly with the patient. Illness related factors include severe illness leading poor insight into their illness and the need to take medications. Medication related factors include like the complexity of the regimen, and duration of the course. Regimens that require disruption to lifestyle, or special techniques or arrangements are less convenient and may lead to refusal or poor adherence [52].

4. Future directions

Long acting anti-psychotic formulations have helped patients with psychosis. The depot formulations have been known to be helpful in improving compliance and thus the overall course and prognosis of the illness. There is a need for developing antidepressants and other psychotropic drugs in injectable depot formulations which can improve compliance and hence decrease chances of relapse. Another important area of potential research and development is the implantable internal drug delivery systems. These are being developed by application of microtechnology and nanotechnology. There has been research into the development of implantable delivery system using silicon microchip. The microchip combined with microreservoirs of drugs could allow for on-demand controlled release of single or multiple drugs. Such delivery systems can be expected to resolve patient compliance issues and also improve the ability to maintain a more constant plasma drug level which in turn could lead to better tolerability and more consistent drug action [53].

These preparations will not only be helpful in those who suffer from recurrent major depressive episodes or long standing anxiety disorders but they can also help in medically debilitated populations where oral formulation cannot be prescribed as well as patients who refuse to take oral medications.

5. Conclusion

Dependence on oral medications for the treatment of depression remains a major barrier to effective treatment for some patients especially those who are medically debilitated. Slowly we are evolving new treatments and delivery systems that will ultimately make treatment possible for this subset of patients.

With rapid development in the field of psychopharmacology, we now have some options in our delivery systems for antidepressants. Increasingly nontraditional methods of delivery make it possible to effectively treat those with comorbid medical and depressive conditions. However, we still need newer medications as well as newer formulations of existing medications so that we are able to more effectively treat depression in co-morbid medical conditions that limit the usage of conventional anti-depressants.

6. Summary

- Psychiatrists are often faced with the challenge of finding an adequate alternative when they want to prescribe anti-depressants to a

patient who is not physically capable of taking pills secondary to gastrointestinal dysfunction or a patient who simply refuses to take pills.

- Commercially available options in the US and many countries in the world are limited; though few, there are some alternative options. IV or IM formulations are still mostly experimental.
- The alternatives commercially available and FDA approved are mirtazapine and selegiline orally disintegrating tablets (ODTs) and selegiline transdermal system (STS).
- ODTs primarily get absorbed into the body by several pathways. They are usually taken without water and once in the buccal cavity they disintegrate rapidly in saliva, usually in a matter of seconds.
- The STS (Emsam) is the only FDA approved transdermal delivery formulation for major depressive disorder. Selegiline gets directly absorbed into the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism.
- Ketamine, an anesthetic agent, is an off-label drug that may open therapeutic avenues in the future. Based on several studies, it has shown much promise and potential in treatment of depression. It also provides the option of IV and IM administration.
- Routes of administration for anti-depressants that still remain in experimental stages include IV, IM, inhalational, intranasal, sublingual, and rectal.
- There is a need for development of other alternative formulations such as long acting injectable and implantable antidepressants.

Conflict of interest

None.

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Appendix A. Supplementary data

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