Review

Psychopathology and psychopharmacology: which patients may benefit more from antidepressant oral drops than from antidepressant oral tablets? The case of paroxetine

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SUMMARY

This article examines the therapeutic benefits of oral antidepressant solutions as an alternative to standard tablet forms for the treatment of depressive and anxiety disorders, using paroxetine oral drops as an example. Paroxetine, a selective serotonin reuptake inhibitor (SSRI), is commonly prescribed for anxiety and depressive disorders, and the oral drop formulation may offer significant advantages for certain patient populations. Patients who may benefit from this formulation include those who have difficulty swallowing tablets, those who are more sensitive to side effects and those who require gradual and individualised dose titration. This article discusses the unique pharmacological properties of Paroxetine Oral Drops, highlighting their role in improving patient adherence, minimising perceived or feared side effects, and providing tailored dosing flexibility. In addition, a clinical case of a patient with depression and comorbid anxiety is presented to illustrate how paroxetine oral drops can effectively address complex clinical needs. The findings support the utility of paroxetine oral drops in personalised antidepressant therapy, particularly for patients who may have difficulties with tablet forms. Further research is recommended to investigate the comparative efficacy, tolerability and patient adherence of liquid and tablet SSRIs in different clinical subgroups.

Key words: drops, liquid, formulation, antidepressant, tablet, pill, paroxetine

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How to cite this article: Fagiolini A, Pinzi M, Koukouna D, et al. Psychopathology and psychopharmacology: which patients may benefit more from antidepressant oral drops than from antidepressant oral tablets? The case of paroxetine. Journal of Psychopathology 2025;31:18-24. https://doi.org/10.36148/2284-0249-N723

Introduction

Depressive and anxiety disorders are among the most common illnesses worldwide, and antidepressants are a cornerstone of treatment. While oral tablets are the most used form of antidepressant administration, oral drops offer an alternative formulation with distinct advantages for certain patients. Patients who may benefit from oral drops include those who have difficulty swallowing tablets, such as the elderly; patients who require slow titration, such as those who are highly concerned about medication side effects, which is common in patients with anxiety; patients who want to limit the risk of withdrawal symptoms when a medication is discontinued; etc.

This paper examines the clinical profiles of individuals who may benefit more from oral drops than from oral tablets, focusing on paroxetine, a selective serotonin reuptake inhibitor (SSRI) approved in Europe for major depressive disorder, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, social anxiety disorder, and post-traumatic stress disorder. By comparing the benefits of oral drops and tablets, we identify which patient populations may have better outcomes with the oral solution formulation. We also provide a case study to demonstrate how the issues reviewed and discussed can be translated into clinical practice.

Comorbidity of depression and anxiety and patient concerns with antidepressants

It is well documented that depression and anxiety often co-occur, adding complexity to the treatment of these disorders. Many patients with comorbid depression and anxiety express significant concerns about initiating antidepressant therapy, particularly with regard to doses that they perceive as "too high" or potentially harmful. These patients often report fears of experiencing side effects such as gastrointestinal upset, dizziness, allergies, or other adverse effects. Another common fear relates to swallowing tablets, where patients worry about choking or feeling a tablet stuck in their throat.

For patients who are particularly anxious about starting antidepressant therapy, oral drops may be a more appropriate alternative to traditional tablets. Oral drops offer the flexibility of starting at very low doses and slowly titrating the medication upward based on the patient's tolerance. The ability to taper the medication also minimizes the potential for withdrawal symptoms, once the medication is discontinued. This slow and flexible titration process, coupled with the perception of reduced risk of side effects, often makes oral drops a more acceptable option for patients who are highly sensitive or fearful of medication-related side effects.

Psychopathology of depression and anxiety disorders and psychopathological traits that may be associated with higher acceptance of antidepressant oral drops compared to tablets

Major depressive disorder (MDD) is a chronic and debilitating illness whose pathophysiology involves disturbances in neurotransmitter systems, particularly serotonin, norepinephrine, and dopamine [1]. Paroxetine, like other SSRIs, works primarily by inhibiting serotonin reuptake, improving mood regulation, and alleviating depressive symptoms [2]. Studies have demonstrated its efficacy in the treatment of moderate to severe depression, for instance in individuals with melancholic features [3].

Anxiety disorders often co-occur with depression, which complicates treatment. Paroxetine has been shown to be effective in treating both conditions, making it an appropriate option for individuals with anxiety disorders such as panic disorder (PD), generalized anxiety disorder (GAD) and social anxiety disorder (SAD) [4,5].

Advantages of oral drops compared to tablets

1. Precise dosing flexibility

Oral drops allow for gradual and precise dose adjustment, which is particularly useful for patients who are sensitive to medication or who require gradual dose titration to avoid side effects. In contrast, tablets are available in fixed doses, which may not always be appropriate for patients who require fine-tuned dosing [6]. This is particularly useful when starting, stopping or adjusting a medication. In fact, using the oral solution may allow for a very gradual increase or decrease in dose, reducing the risk of side effects from the more rapid increases or decreases that are inevitable with fixed-dose tablets.

2. Ease of administration

Oral drops are easier to administer to patients who have difficulty swallowing pills, such as those with dysphagia or neurological conditions such as Parkinson's disease or stroke. These patients often struggle with pills, leading to poor adherence unless alternative formulations are provided [7].

3. Faster absorption

Oral drops may be absorbed more quickly than tablets, as they bypass the dissolution phase in the stomach. This can lead to faster onset of therapeutic effects, which is particularly beneficial for patients in acute distress, such as those experiencing panic attacks or severe anxiety [2]. However, paroxetine oral solution is primarily designed for gastrointestinal absorption, and there is no substantial evidence to suggest that it is significantly absorbed through the sublingual route. Sublingual administration relies on the high vascularity under the tongue, but paroxetine's molecular properties (relatively high molecular weight and low lipophilicity) make it less ideal for rapid sublingual absorption. Most of it is therefore likely absorbed in the stomach and intestines after being swallowed with saliva. For sublingual absorption, drugs generally need to be both lipophilic and of lower molecular weight, characteristics that favor quicker diffusion across the sublingual mucosa. Since paroxetine lacks these properties, its effectiveness and bioavailability are unlikely to be impacted by stalling it in the mouth rather than swallowing it directly.

4. Reduced gastrointestinal disturbance

Some patients experience gastrointestinal side effects, such as nausea or irritation, when taking tablets. Oral drops are a gentler option for these individuals, as they bypass the need for dissolution in the stomach, reducing the risk of gastrointestinal discomfort [6]. This is particularly important for patients with pre-existing gastrointestinal conditions.

5. Improved adherence in special populations

Patients like geriatric, neurological, and cognitively impaired patients often struggle with adhering to a tablet-based regimen. When appropriate, oral drops can be mixed with food or beverages, making administration

easier and improving adherence, particularly in vulnerable populations [7]. Interestingly, Zanardi and colleagues found increased adherence when patients were treated with paroxetine oral solution compared to patients treated with paroxetine tablets [8].
Table I provide some practical examples of clinical situations when oral drops may be particularly useful.

TABLE I. *Examples of Clinical Situations when Oral Drops may be particularly useful.*

Examples of Clinical Situations when Oral Drops may be particularly useful
1. Difficulty swallowing tablets: Patients with dysphagia (difficulty swallowing) or those who struggle with pill size may prefer drops for easier ingestion.
2. Variable or flexible dosing needs: Drops allow for precise, adjustable dosing, which can be especially helpful for patients who require gradual dose titration, such as children, the elderly, or those who are sensitive to side effects.
3. Rapid absorption: In liquid form, some antidepressants are absorbed more rapidly, potentially offering a faster onset of action, which may benefit patients who need faster symptom relief or who struggle with delayed absorption issues.
4. Nausea or gastrointestinal issues: Drops may be gentler on the stomach than solid tablets, so patients with GI issues may tolerate liquid forms better.
5. Children or geriatric patients: Children and older adults often require individualized dosages, which oral drops can easily accommodate, making administration easier and more accurate.
6. Medication aversion: Some patients who are reluctant to take medication may find the liquid form less intimidating than pills, improving adherence.
7. Need for flexibility and a very gradual increase or decrease in dose. Some patients require very gradual increases or decreases in dose to avoid withdrawal symptoms, which is easier to achieve with oral drops than with fixed-dose tablets.

Limitations of oral drops (and oral solution) versus oral tablets

While antidepressants in oral drop form provide notable advantages for certain patient populations, they also present some limitations when compared to conventional tablets. These disadvantages are essential to consider for comprehensive, patient-centered treatment planning.
One of the primary limitations of oral drops is the complexity and inconvenience of dosing. Unlike tablets, which offer fixed doses and are easy to measure, oral solutions require careful counting of drops to achieve the prescribed dose. This process can lead to dosing errors, especially in patients with visual impairments or cognitive limitations, thereby affecting the efficacy and safety of treatment [8]. Additionally, administering the correct dose of liquid antidepressants can be more challenging in low-light or non-clinical settings, where patients might lack the necessary tools to measure precisely.
Also, oral drops are generally less portable and stable than tablets. Liquid formulations often require specific storage conditions and may be more susceptible to degradation under variable environmental conditions, such as heat or exposure to light [6]. In contrast, tablets are compact, more resistant to changes in temperature and humidity, and easier to transport. This difference can impact adherence, particularly in patients who travel frequently or live in environments where controlled storage is challenging.
An additional disadvantage of oral solutions is that they may have an unpleasant taste, which can reduce adherence, especially in sensitive individuals or younger patients [1]. Unlike tablets, which can often be swallowed quickly and without lingering sensory effects, oral drops must remain in the mouth briefly and may leave a residual aftertaste, leading some patients to avoid consistent use. This sensory factor has been cited as a reason for poor adherence in patients prescribed liquid medications, especially when alternative tablet forms are available [8]. Lastly, In many healthcare systems, liquid formulations of medications are more expensive than tablets, due to production complexity and lower demand [5].

Clinical Case - Paroxetine oral drops

Patient history

David, a 30-year-old man, is married and the father of a 2-year-old child. He has worked in an agricultural company since the age of 20. Over the past six months, David has experienced significant changes in his physical and mental health. Once an active and sociable individual, David has become increasingly apathetic, tired, anxious, and discouraged. His wife reports that he has become quiet, withdrawn, and easily irritable - traits that were not part of his personality before.
David describes feeling “empty” and constantly sad for no apparent reason. In the morning, he struggles to get out of bed, feels a heaviness in his legs, and has a lack of energy to the point that it takes him much longer to get ready for work than before. In addition, David reports a mixture of restlessness and tension on the one hand and a marked psychomotor slowing on the other. He takes longer to complete daily tasks and feels “slow and anxious” both physically and mentally. His colleagues have noticed a decrease in his efficiency and ability to make quick decisions.

Another disturbing symptom is chronic fatigue: David feels constantly exhausted, even after a good night's sleep. This pervasive fatigue prevents him from being as active as he once was. His previously busy days are now filled with inactivity and passivity, and David prefers to spend his free time on the couch, often trying unsuccessfully to take a nap during the day.

In addition to fatigue, sadness, and psychomotor slowing, David has noticed changes in his eating habits. Unlike the typical loss of appetite often associated with depression, David has experienced a significant increase in appetite, especially for sweets and carbohydrates. Although he reports no pleasure from eating, he has gained about 6 kg in the last three months, which has further worsened his mood by increasing feelings of inadequacy and guilt. David feels frustrated and anxious about his inability to manage his eating, leading him to isolate himself further and avoid social Situations in which he fears being judged for his changing appearance.

Work, already stressful due to an increased workload, has become unbearable. David experiences anxiety attacks at work, with heart palpitations, tremors, and feelings of suffocation. The thought of having to work 8 hours a day with other people who might see his panic attacks terrifies him. To avoid these situations, David has taken more sick days, which has led to conflicts with his supervisor and worsened his self-esteem.

Family and personal history

David has no psychiatric history, although he describes himself as an anxious person who tends to worry. However, his mother suffered from recurrent depression and his older brother had a history of alcohol abuse. David has never used illicit substances and his alcohol consumption is moderate and limited to weekends. Physically, he has no chronic diseases other than mild hypertension, which was diagnosed two years ago and is well controlled with an ACE inhibitor.

Initial assessment and diagnosis

David has been seen by his primary care physician, who refers him to a psychiatrist for further evaluation. During the psychiatric visit, David appears visibly tired, has a slumped posture, and speaks slowly. He expresses feelings of deep sadness and helplessness and describes his life as "an unbearable burden". He admits that he no longer finds pleasure in activities he once enjoyed, such as watching soccer games or spending time with friends. His lack of interest and motivation dominate his symptoms, but he also experiences significant tension, anxiety, and restlessness.

Given these symptoms, David is diagnosed with Major Depressive Disorder, severe episode, with anxious and atypical features, according to DSM-5 criteria. The atypical features include increased appetite and psychomotor retardation, along with marked anxiety. David has been informed that his condition is treatable, but requires time and a combination of pharmacological and psychological support. David expresses concern about starting medication, fearing side effects and feeling that the pills might "stick in his throat" or "choke" him.

Treatment plan

Given David's clinical picture, his psychiatrist decides to start him on paroxetine oral drops, an SSRI used to treat both depression and anxiety. Paroxetine is chosen because of its effectiveness in treating depression with comorbid anxiety. David is reassured by the option of oral drops, as he was afraid of choking on pills, and is reassured that starting at a low dose would minimize the risk of side effects.

Treatment begins with 10 mg (10 drops) per day for the first week, with the goal of gradually increasing to 20 mg (20 drops) in subsequent weeks, depending on David's clinical response and tolerance.

David is informed that it may take several weeks to experience the full benefits of treatment and that mild side effects such as nausea, headache, or a temporary increase in anxiety may occur. Zolpidem 10 mg is also prescribed as needed for insomnia, with instructions to use it only for short periods of time.

First phase of treatment

After one week of treatment, David returns for a follow-up visit. He reports a slight improvement in his anxiety, especially in work situations, but persistent fatigue and psychomotor slowing. It is decided to increase the paroxetine dose by 5 drops per day, up to 20 mg (20 drops) per day. During this period, David experienced only mild gastrointestinal side effects, such as mild nausea, which quickly resolved without treatment.

His wife noticed that he seemed a little less irritable, but his fatigue and social withdrawal persisted. The psychiatrist encourages him to continue therapy, stressing that full improvement may take longer.

Evolution after three weeks

After three weeks, David reported further improvements in his mood. Although fatigue and psychomotor slowing remain, he is able to perform daily tasks more effectively. The frequency and intensity of his anxiety episodes have decreased, and David is able to attend work without experiencing panic attacks. He has also noticed improved sleep and has stopped taking zolpidem. Although his fatigue has not completely disappeared, he has more energy in the morning.

His increased appetite persisted, but David has become more mindful of his eating habits and is trying to manage his weight, albeit with some difficulty. It is rec-

ommended to increase the paroxetine dose by another 5 drops per day, up to 40 mg (40 drops) daily, and to integrate the pharmacological treatment with cognitive-behavioral therapy (CBT) to better manage stress and work on emotional regulation.

Side effects

After eight weeks, David had fully recovered from the acute phase of his depression. He reports feeling "better than ever," and no manic symptoms have been observed. David mentions delayed ejaculation, but does not find it frustrating - in fact, he considers it an advantage, as he previously suffered from premature ejaculation. David asks how long he needs to continue treatment.

Long-term management

The psychiatrist discusses the need to continue the treatment for at least 6-12 months as he has just come out of his first depressive episode. David agrees to continue the medication, given the benefits he has experienced and the fact that he has started to lose weight thanks to a more controlled diet and the resumption of regular physical activity. David mentions that he has taken up swimming and cycling again, finding that these activities contribute greatly to his well-being.

It is decided to continue paroxetine at 40 mg/d and to evaluate tapering or discontinuation after 6-9 months of stability. CBT is continued given its benefits in addressing negative thoughts, residual anxiety, and stress management.

David responded positively to treatment with paroxetine drops for his depression with anxious and atypical features. He achieved a significant improvement in his quality of life and daily functioning. The combined approach of pharmacotherapy and psychotherapy helped stabilize his condition, improve his ability to cope with stress, and regain control of his life.

Discussion

The use of paroxetine oral drops presents a compelling alternative to standard tablet forms for specific patient populations, especially those who exhibit sensitivities to medication side effects, have difficulties with traditional pill-based administration, or require highly individualized dosing. This alternative formulation offers unique benefits, primarily in flexibility and patient-centered management of antidepressant therapy, which are particularly valuable for patients with both depressive and anxiety disorders.

One of the principal advantages of paroxetine in oral drop form lies in its potential to improve adherence, particularly among populations who struggle with swallowing pills or fear potential side effects. Previous studies have highlighted that adverse effects and difficulties in medication administration are among the primary reasons patients may discontinue or resist treatment [6,8]. Patients such as David, whose clinical history suggests a strong aversion to pill-based medication, likely benefit from the flexibility offered by oral drops. This formulation allows for titration in very small increments, which can significantly reduce the anxiety associated with initiating treatment, as it provides a sense of control over potential adverse reactions and dose adjustments [4,5].

In David's case, the option to titrate slowly proved to be a practical and psychologically supportive strategy, addressing both his anxiety about the medication itself and his underlying anxiety disorder. Furthermore, the ability to adjust doses precisely is a key factor when treating patients with anxiety disorders, as the slow and careful titration can prevent sudden increases in anxiety levels, which are sometimes reported in initial phases of antidepressant therapy [2].

In some cases, the pharmacokinetic properties of oral drops provide an additional level of benefit when a faster onset of action is desired. Because oral drops bypass the dissolution phase required by tablets, they may allow for more rapid absorption and onset of action, which is particularly beneficial in the treatment of acute anxiety symptoms [2,3]. However, more research is needed to determine how much of this effect is pharmacologically meaningful and how it might differ between different SSRI options [2,6].

Although paroxetine is not subject to significant sublingual absorption due to its physicochemical properties, the solution formulation still offers advantages in terms of the possibility of a slower and more individualized titration and is particularly helpful for patients like David who are concerned about side effects of medication and are reassured by a very low starting dose and titration schedule. In addition, anxious patients are often concerned about the risk of choking on tablets and therefore often prefer a liquid formulation.

Gastrointestinal side effects such as nausea and abdominal discomfort are common reasons for early discontinuation of SSRIs [6]. The use of oral drops, which may reduce irritation by avoiding a high concentration in a small area of the stomach (i.e., the area that comes in contact with the tablet), may therefore be a preferable option for patients with pre-existing gastrointestinal problems or sensitivity. As a result, paroxetine in oral drop form may be gentler on the GI tract, allowing for improved tolerability and reducing the likelihood of early discontinuation due to adverse effects. This is consistent with David's experience of only mild nausea that resolved rapidly, likely influenced by the gradual dose increase.

The co-occurrence of anxiety and depressive disorders

presents additional treatment challenges, as pharmacological treatment must address the symptoms of both conditions simultaneously. The efficacy of paroxetine in treating both depressive and anxiety symptoms is well documented, with studies supporting its use across a range of anxiety disorders, including social anxiety disorder, panic disorder, and generalized anxiety disorder [4,5]. For patients like David, who experience severe anxiety along with depressive symptoms, paroxetine offers a dual-action solution that may be particularly beneficial. In addition, the precise dosing capabilities of the oral drop formulation allow for a highly individualized treatment plan, which can be critical to achieving optimal symptom control without the risk of overmedication or undertreatment.

Cases like David's highlight the importance of alternative antidepressant formulations in personalizing mental health treatment. While paroxetine tablets remain a standard, effective choice, oral drops offer a greater degree of flexibility that may be critical for patients with unique treatment challenges. Future research should further investigate the comparative effectiveness of SSRIs in liquid versus tablet form, particularly in terms of efficacy, tolerability, patient adherence, and speed of symptom relief.

Conclusions

In conclusion, paroxetine oral drops represent an important tool in the psychopharmacological management of patients with depressive and anxiety disorders, particularly for those with aversions to tablets or specific needs for tailored dosing. Large, controlled trials and studies could clarify the specific advantages of oral drop formulations in different patient subgroups, thereby guiding clinical decision making in the selection and administration of antidepressants.

Take Home Points

1. Patient suitability: Paroxetine Oral Drops may be particularly useful for patients who require individualized dose adjustment, who are highly sensitive to (or fearful of) side effects, as is often the case in patients with anxiety disorders, or who have difficulty swallowing tablets. This formulation allows for precise titration, which may reduce the anxiety associated with dose adjustments and improve adherence in these populations.
2. Improved tolerability: The oral drop formulation may minimize side effects such as gastrointestinal discomfort, a common problem with tablet forms, by allowing for lower initial doses and reducing direct gastric exposure. This may make treatment more acceptable to patients prone to gastrointestinal side effects.
3. Improved adherence in special populations: Elderly, neurologically impaired or anxious patients, who often have difficulty with pills, may find oral drops more manageable, improving their adherence to treatment.
4. Case Evidence: A clinical case demonstrates that paroxetine oral drops effectively treat complex symptoms of depression and anxiety, providing gradual relief while alleviating patient concerns about side effects and pill aversion.
5. Future Research Needs: Additional research is war
6. ranted to further investigate the efficacy, tolerability, and patient adherence between antidepressant liquid and tablet formulations, particularly in various clinical subgroups.

Funding

Unrestricted grant from Angelini Pharma S.p.A.

Conflicts of interests statement

Andrea Fagiolini is /has been a consultant and/or a speaker and/or has received grants from Angelini, Boheringer Ingelheim, Idorsia, Italfarmaco, Lundbeck, Janssen, Medicamenta, Mylan, Otsuka, Pfizer, Recordati, Rovi, Sunovion, Teva, Viatris

Alessandro Cuomo is /has been a consultant and/or a speaker and/or has received grants from Angelini, Italfarmaco, Lundbeck, Janssen, Otsuka, Recordati, Rovi, Teva, Viatris

All other authors have no conflicts of interest.

Authors contribution

All Authors contributed to the drafting and critical revision of the manuscript.

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