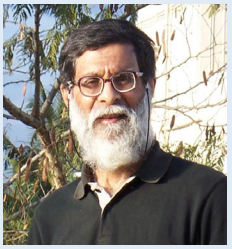
Clinical and Practical **Psychopharmacology**

Sustained-Release, Extended-Release, and Other Time-Release Formulations in Neuropsychiatry

Chittaranjan Andrade, MD



Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

Pills and capsules may release their contents within minutes of ingestion; these are *immediate-release* formulations. Pills and capsules may also release their contents after a time lag, or a little at a time, or in some other predetermined way; these are *time-release* formulations. Many drugs in psychiatry have been time-release formulated to reduce their local adverse effects in the gastrointestinal tract, to reduce adverse effects associated with peak blood levels, or to artificially extend their half-life. Time-release formulations are associated with the added advantages of convenience of dosing, improved compliance, and less fluctuation in blood levels across the course of the day. A disadvantage of time-release formulations is that they may be incompletely absorbed; this is a serious issue in patients with acute or chronic intestinal hurry disorders, such as gastroenteritis or irritable bowel syndrome. Time-release formulations may also be more expensive than immediate-release formulations.

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Introduction

Most orally administered medications are pills and capsules that dissolve within minutes after swallowing; that is, they are *immediate-release* formulations. Other formulations dissolve more slowly and in different ways; these are *time-release* formulations. This article examines the applications, advantages, and disadvantages of time-release neuropsychiatric drug formulations that are available in different parts of the world. Some practical issues are also considered.

Time-Release Formulations: Applications

Most drugs are immediate-release formulations; the tablet or capsule dissolves within minutes of ingestion. Absorption of the contained medication is commonly complete in 2–3 hours and is associated with peaking of blood levels of the drug. The blood drug levels thereafter gradually drop as the drug is metabolized and eliminated. Sometimes, there may be reasons why physicians may want to slow down this sequence of events, and this becomes possible through the use of time-release formulations, as discussed below. Importantly, whereas the arguments for the time-release formulation appear reasonable in each case, evidence does not necessarily exist for the posited advantage(s) of each marketed formulation.

Avoidance of local effects in the stomach. If a drug causes nausea, gastric irritation, or other adverse reactions because of local effects in the stomach, such adverse effects can be diminished by presenting the drug in an enteric-coated or delayed-release form. Such a formulation will remain intact until it reaches the alkaline medium of the small intestine, where it dissolves to release the active drug. In other words, instead of "immediately releasing" upon entry into the stomach, the medication "immediately releases" upon entry into the small intestine. The time lag for release is anywhere from 15 minutes to 2 hours, depending on whether the medication is taken on an empty stomach or with food and depending on how the pill is formulated. Absorption of the drug and peaking of blood levels are correspondingly delayed because of the delay in the disintegration of the formulation in the gastrointestinal (GI) tract; this property, in fact, is characteristic of all time-release formulations. Valproate is an example of a medication that may be formulated as an enteric-coated or delayed-release drug.[1] Enteric-coated aspirin is also available, but its advantages remain in dispute.[2]

Avoidance of local effects in the gastrointestinal tract. If a drug causes local adverse effects for a greater distance along the GI tract, the risk of such adverse effects can be reduced by formulating the medication to periodically release in small packets during its transit through the gut. This way, less of the drug is available to act on local tissues at any given point in time; so, because drug adverse effects are usually dose-related, the local adverse effects diminish. As an example, when paroxetine is administered as a controlled-release formulation, its GI adverse effect profile and tolerability improve.[3–6] It is not clear, however, whether this benefit is due to the enteric coating or due to

Clinical Points

- Time-release drug formulations release their contents after a time lag, or a little at a time, or in some other predetermined way.
- Advantages of time-release formulations include 1 or more of the following: reduced local adverse effects in the gastrointestinal tract, reduced adverse effects associated with peak blood levels, artificially extended half-life, convenience of dosing, improved compliance, and less fluctuation in blood levels across the course of the day.
- Disadvantages of time-release formulations include one or both of the following: incomplete gastrointestinal absorption, especially in patients with acute or chronic intestinal hurry syndromes, and increased cost of treatment.

the controlled-release formulation in addition to the enteric coating.

Blunting of peak blood levels of the drug. If rapid absorption of a drug results in rapid rise in blood levels of the drug and hence adverse effects related to the high levels, the risk can be reduced by formulating the drug as a sustained-release or extended-release formulation. In such a formulation, the release of the drug and hence its absorption will be slow. This will result in a lower peak blood level and hence a lower risk of associated adverse effects. As an example, bupropion can be dosed as a 300-mg pill only when it is in an extended-release form; in immediate-release form, such a single high dose will result in a spike in the blood level and the risk of a seizure.

Blunting of prolonged high blood levels of the drug. If blood levels of a drug remain high for a long time, the experience of associated adverse effects is prolonged. This risk is reduced when the absorption of the drug is slowed and when peak blood levels are consequently blunted, such as through the use of a sustained-release drug formulation. As an example, if a patient takes 150 mg of immediate-release clomipramine at bedtime, he may have a dry mouth and a hangover for much of the next morning because the blood level of the drug is still high. However, if the same dose of the drug were to be administered in sustained-release form, the blood level peak would lower, and it is less likely that the blood level in the morning would cross the threshold for triggering adverse effects. Similar considerations might improve the tolerability of quetiapine, which is available in both sustained-release and extended-release formulations in addition to the immediate-release formulation.

Prolongation of duration of action. If a drug has a short half-life, there will be a rapid fall in the blood level of the drug as the drug is metabolized and eliminated. This fall in blood level may be associated with a loss of efficacy of the medication (eg, as with carbamazepine in seizure disorder), or even with symptoms of drug withdrawal (eg, as with venlafaxine in anxiety or depression). So, the drug will need to be administered at frequent intervals for uniform blood levels to be maintained. Sustained-release formulations of drugs with short half-lives obviate the need for repeated intraday dosing by allowing the administration of a larger dose per dosing occasion.

As an example, buspirone has a short half-life and is usually administered 2–3 times a day; extended-release buspirone can be administered in a higher dose, once daily.[7] In this context, although alprazolam has an intermediate half-life of about 12–15 hours,[8] it may need to be administered up to 3 times a day because of the wearing off of therapeutic action in patients with generalized anxiety or panic disorder. In sustained-release form, this drug can be administered in a single large dose just once a day.[9] As yet another example, the efficacy of zolpidem quickly wears off because the drug has a short half-life of 2–3 h[10]; sleep maintenance and total sleep duration can be improved by administering the drug as an extended-release formulation.[11,12]

Note that although the metabolic half-life of the drug remains the same, time-release formulations increase the effective half-life of the administered dose.

Nomenclature

Across the world, a number of suffixes are used to identify time-release formulations, including *TR, DR, SR, CR, ER, XR,* and *XL*. *TR* nonspecifically indicates time-release; propranolol has been marketed as a TR formulation. *DR* indicates delayed-release, as in enteric-coated tablets; valproate is an example of a drug that is available as a delayed-release formulation. *SR* indicates sustained-release; this is a rather generic term that is used to describe gradual release in the formulations of drugs that include alprazolam, bupropion, clomipramine, quetiapine, and others. *ER, XR,* and *XL* indicate extended-release in what is usually a once-daily dosing formulation. Divalproex and quetiapine are available as ER, venlafaxine as XR, and bupropion as XL once-daily formulations.

CR indicates controlled release along with the special property of the release following a specific, predetermined pattern.[13] An example is a drug for colon cancer that is specifically meant to release in the large intestine.[14]

Note that drug names may have suffixes that indicate other characteristics, too; for example, *MD* may refer to "mouth-dissolving" tablets, and *MT,* to "melt tablets."

Formulations

There are dozens of ways in which drugs can be formulated to achieve the desired property of release,[13,14] some of which may even characterize the name of the formulation, as with methylphenidate OROS (osmotic controlled-release oral delivery system).[15] The formulation may comprise single units such as capsules, coated tablets, insoluble matrix tablets, soluble matrix tablets, or degradable matrix tablets, or it may be made of multiple units in such forms as granules, microcapsules, and beads.[13] A technical discussion on formulation is out of the scope of the present article.

In the early era of time-release formulations, the entire tablet was formulated in concentric layers of medication alternating with barrier layers; as a barrier gradually dissolved, it released the medication layer below it and

exposed the next barrier layer. In later types of formulation, individual granules of medication were barrier-coated in such concentric layers. Present-day formulations are more complex.

Most time-release formulations lose their time-release property and become immediate-release formulations if the integrity of the pill or capsule is damaged; this is why the manufacturer may recommend that the medication be swallowed whole without chewing, breaking, or crushing. Therefore, most time-release formulations cannot be chewed and swallowed by patients who have difficulties in swallowing, or powdered and administered with food, or powdered and administered through a nasogastric tube.

If individual granules of a time-release pill are barrier-coated, as described earlier, then even if the pill is broken and administered, each piece of the pill will retain the time-release property of the parent pill. As an example, at least 1 sustained-release alprazolam formulation has this property. As an example, extended-release memantine capsules can be opened and their contents sprinkled on food.[16] The manufacturer's description of the formulation in the supporting literature (available in the pill pack or online) will allow the physician and patient to know how a particular formulation can be used. If supporting literature is not available, the only way of finding out is to obtain the information directly from drug company representatives.

Other characteristics of the formulation, such as whether it is a 12-hour formulation or a 24-hour formulation, and how much of the drug is released, where, and when, would also be described by the manufacturer in the supporting literature. Physicians need to be aware of this information in order to know how best to prescribe the drug.

Advantages of Time-Release Formulations

Some of the advantages of time-release formulations have already been considered in an earlier section. These include reduction in GI adverse effects, reduction in adverse effects associated with peak blood levels, and extension of the effective half-life of the drug. There are other advantages, too. These are briefly considered here.

Once-daily dosing is feasible with most time-release formulations. This increases the convenience of dosing and can improve drug compliance.[17] For example, taking one 0.75-mg tablet of sustained-release alprazolam in the morning is far more convenient than having to take 0.25 mg of the immediate-release drug thrice a day; an especial advantage is not having to take the afternoon dose in front of friends or colleagues. Taking controlled-release carbamazepine (which can be dosed twice a day, whereas immediate-release carbamazepine would need to be dosed thrice a day) is convenient because it obviates the need for the afternoon dose; if this afternoon dose is forgotten, the patient may suffer a breakthrough seizure should the medication have been prescribed for the management of a seizure disorder. Taking 1 tablet of extended-release valproate at night is easier to remember than taking 1 tablet of the medication twice a day; a morning dose may be forgotten in the hurry to finish the morning's routines before leaving for work.

Sustained-release dosing is also associated with relatively uniform blood levels of the drug across the course of the day; peaks and troughs in blood levels, noticeable with immediate-release dosing, are diminished. The advantage of blunted peaks is that the risk of adverse effects, associated with the peaks, is diminished. The advantage of shallower troughs is that the risk of loss of efficacy (or the appearance of withdrawal symptoms), associated with a fall in blood levels, is minimized. When adverse effects are fewer, compliance is improved.

A special note is that with sustained-release formulations of methylphenidate, the child usually does not need to take an additional dose at school. So, taking a medication in front of peers will not cause embarrassment to the child, and the school dose will not be forgotten or lost or misused by other children. Other advantages of this formulation have also been described.[18]

Disadvantages of Time-Release Formulations

Time-release formulations are associated with certain disadvantages. As a result of the gradual release, in most patients the tablet reaches the colon before complete dissolution. Absorption from the colon is not as good as that from the small intestine. As a consequence, particularly with once-daily formulations, small quantities of medication are excreted unabsorbed in the form of pellets in the feces. This is why, for example, the CR formulation of paroxetine and the ER formulation of divalproex are dosed at 25% higher levels than their immediate-release formulations; in the case of paroxetine, the higher dose is built into the formulation. The cost of therapy with time-release formulations is therefore slightly higher not only because of the cost of the formulation but also because of the need for the extra dose. Whereas incomplete absorption is a problem with most time-release formulations, it does not appear to be an issue with sustained-release and extended-release formulations of bupropion.[19]

In persons with intestinal hurry syndromes, time-release formulations are associated with poor bioavailability because the tablet rapidly reaches the colon and may even be excreted in feces long before dissolution is complete. Time-release formulations should therefore be avoided in patients with chronic intestinal hurry syndromes (such as irritable bowel syndrome). When patients develop transient intestinal hurry syndromes, such as acute gastroenteritis, the prescription should temporarily be shifted from a time-release formulation to an immediate-release formulation until bowel functioning normalizes, lest the efficacy of the medication be lost. Decreased absorption of medication for a few days is rarely a problem in most disorders, but it can be an issue, for example, if the patient is taking the medication for seizure disorder (when lower medication absorption could result in a breakthrough seizure) or if the drug is like

venlafaxine or alprazolam (when drug discontinuation symptoms may manifest).

An important consideration and one that is unresolved in the literature is whether time-release formulations are well absorbed in persons whose normal pattern is to have 2 or more bowel movements spread across the course of the day. If these patients have greater intestinal motility, they may excrete unabsorbed pills faster, resulting in lower bioavailability of the drug. In such patients, then, unless blood levels confirm satisfactory bioavailability, a relapse that occurs may be due to poor absorption rather than to true inefficacy of the medication in that patient.

When large doses of the drug are administered in a single time-release pill, the size of the pill may be large, resulting in swallowing difficulties with some pills and in some patients. At least 1 brand of extended-release divalproex (1,000 mg) suffers from this limitation; as with most other time-release formulations, this tablet cannot be broken because that would destroy its time-release property.

General Notes

The advantages described in earlier sections provoke the thought that all medications should ideally be administered as time-release formulations. This is, however, unnecessary with drugs that have long half-lives because the long-half life itself ensures uniformity of blood levels across the course of the day. For this reason, it is unnecessary to formulate sustained-release aripiprazole. This is also why the need for extended-release memantine is a puzzle. Both aripiprazole[20] and memantine[21] have a half-life of about 3 days.

Time-release formulations may not necessarily do what they are prescribed to do. For example, a sustained-release formulation of clomipramine, administered at night, may merely prolong the duration of the morning hangover instead of preventing it. The physician may then prefer to revert to the immediate-release formulation, or, as a possible strategy, the sustained-release formulation can be dosed in the late evening instead of at bedtime. Similarly, the choice between immediate-release and sustained-release or extended-release formulations of quetiapine will depend on whether it is more important to promote nighttime sleep or to avoid the next-day hangover, and whether the purpose is served by the formulation selected. As with all prescribing, an element of trial and error is inevitable in discovering what works best.

Passing medication shells in the feces does not necessarily imply poor absorption. Sometimes, insoluble parts of a controlled-release formulation may be spotted in the stools; these are known as ghost pills, and they are empty. Ghost pills have been described with several formulations, such as extended-release venlafaxine.[22] There is no way of knowing whether what is spotted in the fecal matter is a ghost pill or an incompletely absorbed pill. Interpretation should be based on blood level assessments, clinical response, and other available information.

Patients who overdose with time-release formulations may experience delayed or prolonged toxicity. This may be seen, for example, with sustained-release lithium[23] and sustained-release clomipramine.[24]

Finally: time-release formulations vary widely in nature and purpose. At the risk of sounding repetitive, it is stressed that physicians who prescribe these formulations should acquaint themselves with the properties of the formulations and the do's and don'ts as described in the manufacturer's literature.

Parting Note

Readers are referred to the review by Keith[25] for a discussion of specific time-release psychotropic formulations.

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