

Methods to Reduce the Anxiety of Mental Disorder Medication

The unprecedented stresses and strains of the last year or so have led to large numbers of people suffering from temporary psychosis or, at the very least, experiencing some form of diminished mental wellness.¹

Imagine the terrifying prospect of having to daily face hallucinations, delusions, and deeply true, deeply isolating, sadness. Combatting such loneliness, anxiety and desperation must be emotionally and physically exhausting. Particularly when there is no apparent end in sight to these feelings.

Welcome to the very real, life-debilitating world of someone suffering from schizophrenia.

Trying to treat someone in this broken mental state is complex. Will they remember to take a tablet? Will they really accept an injection given the extent of their delusional state?

In the words of one sufferer: "Real people with real feelings get schizophrenia. One should never underestimate the depth of their pain, even though the illness itself may diminish their ability to convey it... As one of my own patients told me, 'Whatever this is that I have, I feel like I'm a caterpillar in a cocoon, and I'm never going to get the chance to be a butterfly.'²

In this article we will explore the very real benefits alternative dosage forms, such as oral thin films and transdermal therapeutic systems, bring to the treatment of mental disorders, combining high levels of patient acceptance with effective therapeutic benefit.

Every day, in pharmaceutical companies across the world, thousands of people are committed to delivering better patient outcomes.

Often talked about in depersonalised terms, this 'patient' is the ultimate beneficiary of all manner of workstreams, projects and clinical trials. But how often do

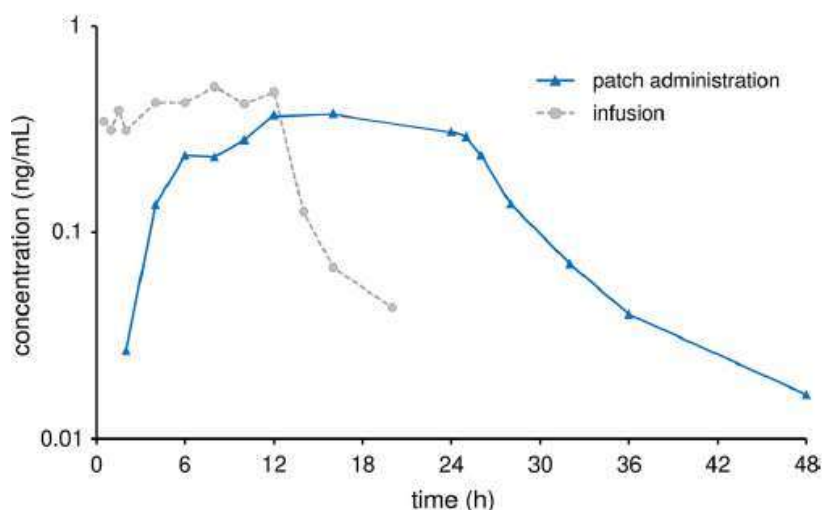


Figure 1 – Mean rotigotine plasma concentrations after application of rotigotine transdermal patch (2mg/24h) or intravenous infusion of 1.2mg over 12h. Adapted with permission from Cawello et.al.

we give thought to the reality of the people behind these theoretical patients? Beyond our understanding of their conditions, symptoms and clinical requirements, to what extent do we consider their emotional state, their hopes and fears, and their experience of medical care?

In the case of mental disorders, this has particular resonance given the variety of barriers that come between patients and successful treatment outcomes. Indeed, the proportion of schizophrenia patients likely to meet the criteria for recovery is estimated to be just 1 in 7. And, while factors such as substance abuse and comorbid psychiatric disorders play their part in influencing this statistic, poor outcomes are most likely to be related to issues around access to treatment, engagement in ongoing care, treatment response, and poor adherence. All these factors are strongly linked to the patient's personal attitude, circumstances and experiences.³

For the answer to why accessing antipsychotic therapies and maintaining adherence remain such significant contributors to treatment failure, it is worth returning to the importance of seeing a patient as an individual. In real-world healthcare settings, each interaction with a schizophrenic patient is highly personal and highly contextualised. It considers a range of interconnected forces that are specific to a particular person and their mental state

at that given time, which might range from overly excited to actively hostile.

Research continues into the wide variety of factors that trigger non-adherence among patients on anti-psychotic drugs. One such factor is the symptom of cognitive impairment, which has been observed to affect most patients with schizophrenia, negatively impacting their ability to register, process and recall information.⁴ Put simply, this means patients with schizophrenia are often, by default, incompatible with sustained adherence programs.

Further contributing factors to non-adherence include the poor levels of insight that patients possess into their own symptoms and their consequences. This lack of awareness often means there is a resulting lack of acceptance of the need to manage symptoms via ongoing treatment.

Treatment may also be rejected by patients who are influenced by the perceived stigma of a mental health diagnosis. Others still may fail to adhere to treatment programs for fear of experiencing unwanted side effects or simply to avoid the discomfort of drugs being delivered by injectable.

Non-adherence is difficult to accurately detect since healthcare professionals (HCPs) are unable to constantly monitor each patient under their care. This means that HCPs are not necessarily equipped

with all the facts they need when making judgements about the effectiveness of a given treatment. This potentially leads to decisions about 'failures' that can trigger unnecessary changes in medication or inaccurate increases in dosage. For patients, non-adherence can result in any number of consequences, from psychotic relapse and hospitalisation to an increased suicide risk.⁵

Where patients are unable to follow a treatment schedule, greater onus is placed on caregivers to support adherence through easy-to-administer therapies outside of a medical setting. And, looking at the factors that positively influence adherence, evidence does suggest that the patient's engagement with their therapy is key. In patients with bipolar disorder for example, studies have found that a collaborative environment, where patients are invested in the management of their own illness, lead to better treatment adherence.⁶

There is potential for innovative drug delivery mechanisms to be used in the treatment of psychiatric disorders, helping to counter many of the existing factors that lead to non-adherence, reduce the burden on caregivers, and support improved patient outcomes.

Transdermal therapeutic systems (TTS) present an increasingly strong case in this context. This category, which has expanded to incorporate a diverse range of patch technologies, features many patient benefits, some of which are amplified in the face of the challenges presented by psychiatric applications.

Non-invasive by design, TTS facilitate the systemic absorption of drug molecules via the skin to give patients and caregivers a simpler, pain-free route to administration. TTS also avoid first-pass hepatic metabolism to enhance the bioavailability of the drug and enable dosing levels to be reduced. With an infusion-like drug release, patients can benefit from reduced dosing frequency, with drug levels controlled by the patch size.

Of particular relevance for patients with mental health disorders, TTS deliver more predictable outcomes through the delivery of sustained, stable plasma medication concentration levels, avoiding the peaks and troughs that can be observed with oral formulations. For caregivers, the sight of a patch also provides visual confirmation of compliance.

Such attributes have led to the development and approval of a range of psychotropic drugs in transdermal delivery forms. These include Rivastigmine, an acetylcholinesterase inhibitor for the treatment of Alzheimer's disease and dementia associated with Parkinson's disease, which has been approved by many regulatory agencies globally, including the US Food & Drug Administration (FDA) and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK.

Further approved therapies delivered via TTS include rotigotine, a dopamine agonist delivered via a once-daily transdermal patch for the treatment of Parkinson's disease; methylphenidate, a central nervous system (CNS) stimulant for the treatment of ADHD;

selegiline, a second-generation monoamine oxidase inhibitor (MAOI) for the treatment of depression; as well as blonanserin and asenapine for the treatment of schizophrenia.⁷

These market references highlight how transdermal technologies have been employed to deliver a sustained dose and support ongoing condition management for patients whose symptoms or situations may compromise adherence.

There are times, however, when patients with mental disorders require immediate treatment over sustained dosing. In acute episodes of schizophrenia, for example, patients may be more aggressive and violent because of psychotic symptoms such as delusions and hallucinations, and the feelings of suspicion and hostility that they trigger. Impulsive actions, including aggression, may also be sparked by the patient's frustration at aspects of their immediate environment.⁸

In these situations, there is a far greater need for medicines to be fast-acting and to be administered via non-invasive routes. The benefits of oral thin films (OTF) are increasingly being explored in this space, since they provide a platform for rapid API uptake in the bloodstream via oromucosal absorption.

As an edible delivery mechanism, OTF do not require the addition of water when being administered and, unlike many oral drug forms, there is very little requirement for active participation on behalf of the patient in terms of chewing or swallowing. The film either dissolves or disintegrates. The simplicity of delivery makes OTF particularly suitable for paediatric and geriatric patient populations, and because they are also able to avoid first-pass hepatic metabolism, bioavailability can be enhanced.

A variety of OTF formats are available, with each aligned to a particular plasma concentration profile. This ranges from fast-disintegrating film, which demonstrates rapid onset but is relatively short-acting, to non-disintegrating buccal film, which provides dosing at a more sustained, lower level. Innovative new formats, such as the FOAM OTF developed by LTS, introduce further benefits, which among others, includes the possibility of delivering higher drug loads, while also presenting in a form that is easy to handle, has a soft mouthfeel and disintegrates quickly.

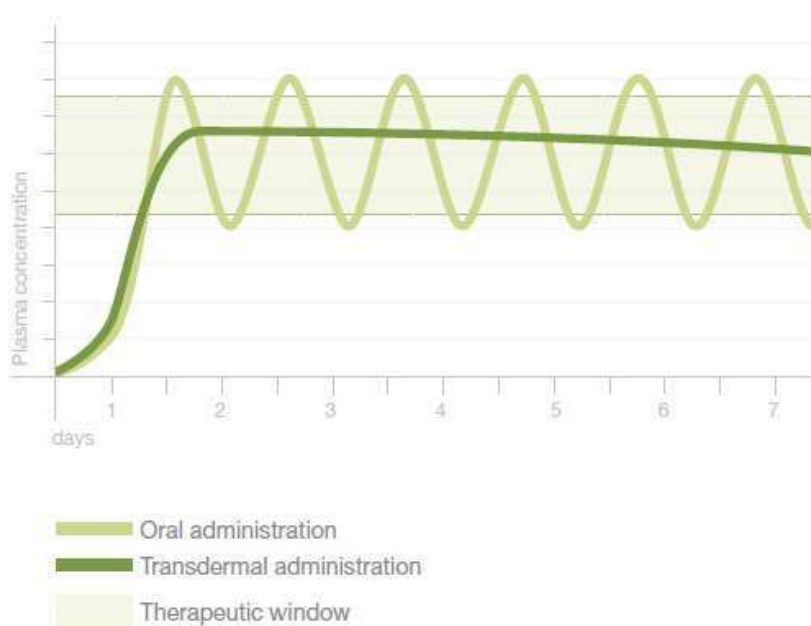


Figure 2 – Infusion like drug release of TTS

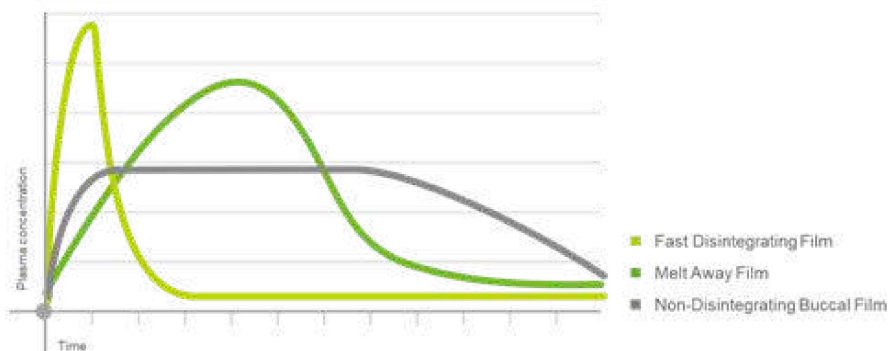


Figure 3 – Modulation of plasma profiles depending on OTF type

A OTF solution has seen notable success in the case of Suboxone, a sublingual film formulation of Reckitt Benckiser’s buprenorphine and naloxone treatment for opioid dependence. Launched with a novel marketing approach in the second half of 2010, the film achieved 55% market share in the US by 2012 and today is the preferred dosage form for buprenorphine and naloxone in the US and Australia.

Beyond this application, the global market for OTF products encompasses treatments for conditions including Alzheimer’s and Parkinson’s disease. Over time, the potential for OTF to tackle mental health disorders will continue to expand just as it will for the use of TTS in the wake of the FDA’s 2019 approval of asenapine in transdermal patch form to treat schizophrenia.

For both these non-invasive drug delivery technologies, API-based innovation will focus on areas such as overcoming solubility challenges and increasing bioavailability for a wider range of drug molecules.

Often, when they are spoken about, patients are framed as passive receivers of treatment,⁹ reflecting the Latin root of the word ‘patients’, which means to suffer or bear. However, in the case of mental disorders, the patient can certainly be active rather than passive at the point therapies are administered.

Agitation, aggression, forgetfulness, confusion and disorientation are just some of the very real, very human, characteristics that must be acknowledged and appreciated to develop innovative therapies that can be delivered in an optimal way.

More personalised therapies for individual patients is a key talking point in our industry today. Taking this truly patient-centric approach to drug delivery ensures therapies will be both actively accepted by the patient in the short-term, while also encouraging the sustained long-term adherence necessary for the enhanced outcomes every individual patient deserves.

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Dr. Patrick Mohr studied pharmacy at the University of Bonn, Germany. He received his Ph.D. in Medicinal Chemistry from the University of Jena with a thesis focussing on development of newly dopamine receptor ligands as potential novel antipsychotics. In 2006 he joined the R&D department at LTS as project lead for the development of several transdermal therapeutic systems including early phase development up to life cycle management. In 2012 he took over the responsibility of a newly founded area focussing on pharmaceutical development of internal projects based on TTS and OTF technologies.

