The use of long acting injectable antipsychotic medication

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Introduction

Soon after the introduction of antipsychotics in the 1950s, poor adherence to oral medication was found to be a critical issue that compromised the efficacy of pharmacotherapy. This stimulated the development of long-acting injectables (LAIs) or "depot antipsychotic injections". The first depot antipsychotic injections were fluphenazine enanthate (1966), and fluphenazine decanoate (1968). Clinical trial results showed a dramatic reduction in the morbidity of schizophrenia for those taking these formulations (Johnson 2009). The next two decade saw an increase of other first-generation LAIs resulting in an important contribution to the development of community psychiatry. In many respects their introduction served to buttress the case for the on-going development of community mental health nursing. Their use also stimulated the development of Depot Clinics where CMHN administered LAIs to dozens of patients in the same day. In these depot clinics however, there was scant interaction with patients and this proved to be a negative outcome of their use. Now that this era is history, the need to administer LAIs provide prospects for a valuable nurse-patient interaction when the nurse can assess the patient's condition, monitor possible side effects and importantly, strengthen engagement with the patient. Therefore, their clinical utility cannot be overstated.

Clinical utility of LAIs

Subsequent surveys and trials of LAIs continued to provide evidence for their benefit (Schooler *et al.* 1980). In landmark study, Hogarty *et al*(1979) demonstrated that, patient relapse rates were significantly better for those taking LAI formulation of fluphenazine (fluphenazine decanoate) than its oral equivalent (fluphenazine hydrochloride). Since then, several studies have continued to report advantages of LAIs over oral antipsychotic medication in terms of relapse prevention and adherence (Lafeuille *et al.* 2014). A meta-analysis of 10 randomised trials showed a significant reduction in relapse rates with the use of LAIs as opposed to oral

formulations (Leucht *et al.* 2011). Further support for their utility comes from a relatively recent meta-analysis of 25 mirror-image studies with 5,940 patients. This study showed LAIs to have strong superiority over oral antipsychotics in preventing hospitalization and decreasing the number of hospitalizations(Kishimoto *et al.* 2013).

In a separate study, Tiihonen *et a*l (2011) reported that the risk of rehospitalisation for patient receiving LAIs was about one third of those receiving oral formulations. Other studies have shown that medication discontinuation rates with oral antipsychotics can reach 74% in comparison to a 33% for second generation depot injection (Marcus *et al.* 2015). Therefore, contemporary evidence seems to support the role of LAIs in the treatment and relapse prevention of those with psychosis. However, caution should be exercised in interpreting these results. This is because comparisons between LAIs and oral antipsychotics are rarely conducted with different formulations of the same medication. Typically, they compare a mix of oral antipsychotics with a mix of LAIs, thus making such comparisons difficult to interpret.

Apart from adherence, discontinuation and relapse issues, LAIs offers other advantages over oral formulations. From a bioavailability perspective, one disadvantage of oral formulations is that they suffer first pass metabolism problems whereas LAIs bypass first pass metabolism in the liver. Bypassing first metabolism allows for a higher proportion of the medicine to be freely available for therapeutic purposes (Samalin *et al.* 2013).

With respect to cost effectiveness, several studies have found LAIs to be more cost effective than their equivalent oral formulations (Llorca *et al.* 2005, Olivares *et al.* 2008, Furiak *et al.* 2011, Druais *et al.* 2016). Therefore, the utilisation of LAIs can result in better clinical outcomes and lower total healthcare costs. In this respect, LAIs may be viewed as a cost saving therapeutic option for patients with psychosis.

The clinical utility of LAIs has not been universally endorsed by empirical research. For example, a systematic review by Haddad *et al* (2009) did not find a clear advantage of LAIs over oral medication. One factor that may explain this discrepancy in findings with previous systematic reviews and meta-analytic studies is that, Haddad et al's study included studies with heterogeneous designs including observational and mirror imaging studies, thus making conclusions difficult. Further, Adams *et al* (2001) conducted a systematic meta-review of Cochrane studies and found first-generation LAIs to have only a slight benefit on global functioning when

compared to oral antipsychotics. The author suggested that the findings were limited by an underrepresentation of patients with poor adherence to oral antipsychotics in randomised controlled studies. In meta-analytic study with a total of 4902 participants, (Misawa *et al.* 2016) found no difference between LAI and oral formulation on side effect burden measures. Overall, the bulk of extant literature support the use of LAI over oral medication in clinically defined situations. Moreover, the process of administering LAI may be viewed as psychotherapeutic intervention.

A previous explorative study found that during the process of giving a depot injection, Community Mental Health Nurses (CMHN) are not only able to give the injection, but be able to carry out an assessment as well as being someone who is dependable, and supportive(Phillips and McCann 2007). Despite the advantages of depot antipsychotics, these formulations remain underutilised in many countries including the UK. One reason why these formulations are under-utilised is that they have not been received enthusiastically by healthcare professional's including nurses.

Resistance from professionals

There are concerns of an increase in side effects and lack of efficacy with their usage although empirical evidence summarised in previous sections does not support these concerns. Initially, their usage was perceived as an attempt by the mental health profession to impose treatment upon patients without due respect to their feelings or human rights. There were also concerns about the potential for medico-legal problems (Glazer and Kane 1992).

This negative attitude towards LAIs is still common particularly in the prescribing of those with first episode psychosis. A survey of 891 European psychiatrists and nurses revealed that 96% preferred depot injection to oral treatment for patients with chronic schizophrenia, whereas only 40% preferred them for first-episode patients (Geerts *et al.* 2013). Further, a systematic review of eight studies reported that LAIs are seen by some health professionals as old fashioned, stigmatizing, causing side effects and being costly(Besenius *et al.* 2010). In cases where clinicians prefer LAI to oral medication, the reasons that they prefer them are, unfortunately, the same reasons that make LAIs unpopular with some patients in the first place. For example, their use in generally seen as a last-resort option for patients with a history of nonadherence.

From an adherence perspective, one important factor that has limited the use of LAIs is that mental health professionals tend to overestimate patient's adherence with oral medication. In this respect, they are inclined to advocate for oral formulations for patients. Moreover, the introduction of second-generation oral antipsychotics (SGA) led to a loss of interest in LAIs due in part to claims of oral SGA's being better tolerated and having less severe side effects (Johnson, 2009). However, it soon became apparent that oral SGAs did not promote better adherence despite the advantages they proffered. The mental health profession's surreptitious reluctance to use LAIs as part of the treatment armamentarium contrast with patients views on these formulations.

Patient's views of LAIs

Several studies have demonstrated that LAIs are welcomed by patients or even preferred (Walburn *et al.* 2001, Phillips and McCann 2007, Iyer *et al.* 2013, Das *et al.* 2014) with at least one study suggesting an unfavourable view (Patel *et al.* 2010). In situations where patients express an unfavourable view of LAIs, this may be because they have not been fully informed of LAIs as a treatment option. Moreover, mental health professionals still have the tendency to make treatment decisions without involving patients despite greater emphasis on recovery-focused care and supported decision-making. In cases where LAIs are offered, patient tend to show a more favourable attitude of LAIs which correlate with their knowledge of these formulations (Potkin *et al.* 2013). This is supported by systematic review of 12 studies by Waddell and Taylor (2009) and several other studies (Heres *et al.* 2007, Patel *et al.* 2009, Waddell and Taylor 2009, Caroli *et al.* 2011, Das *et al.* 2014). According to these findings, patients remarked that that they 'feel better', have a more 'normal life' and find injections 'easier to remember'. The usage of LAIs is beginning to gain attention with the introduction of second generation long term formulation which began in 2003 with the introduction of Risperdal consta.

Since the introduction of Risperdal consta, three additional second-generation antipsychotics have become available in LAI formulation: paliperidone, olanzapine and aripiprazole. They offer similar advantages as first generation LAIs. Like their oral, equivalents, they differ in their side effect profile, storage needs and post-injection observation period. For example, olanzapine depot injection requires a

period of post injection observation. Second generation LAIs also differ from first generation LAIs in the technology that is used to produce the depot effect. Second generation LAIs not only prevent relapses due to treatment interruption, they also achieve more constant plasma levels to reduce side effects. This contrasts with first generation LAIs which can produce inconsistent plasma levels and this can result in increased side effects burden or loss of efficacy. With respect to second generation LAIs, treatment objectives are no longer limited to controlling acute symptoms, they now include the alleviation of negative symptoms and cognitive deficits that are key prognostic factors.

Conclusion

Overall, the use of LAIs offers many advantages but their use has been limited. The reasons for this are manifold and complex. However, one reason frequently cited but based on an inaccurate perception is that, their use in is tantamount to coercion although patients tend to hold a more favourable view of these formulations. The advent of oral second generation antipsychotics which were once purported to be more efficacious further slowed down the use of first generation LAIs. However, the introduction of second generation LAIs has seen interest re-emerge because second generation LAIs offer similar benefits as their oral equivalents. Overall, LAIs may have a place at various stages in the continuum of patient care and they should be one of the options discussed with any patient requiring long-term treatment, even early in the illness course. Many mental health professionals need better education about LAIs and greater familiarity with schizophrenia treatment guidelines.

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