

Knowledge and Attitudes to Relapse Prevention in Schizophrenia Among Clinical Staff - A Limiting Factor in Care Delivery?

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Abstract

Schizophrenia is a relapsing disease. Repeated relapses have detrimental effects on the patient and strains care delivery. Non-compliance with medication is the most common reason for relapse. This questionnaire-based study surveyed the knowledge and attitudes of all groups of staff towards relapse prevention within a single organisation. It finds significant deficits in knowledge, with variations across different classes of care professionals. There was limited evidence of long-term planning and analysis of the evolving risk of relapse due to non-compliance over time. These knowledge deficits are associated with negative cognitive constructs about evidence-based treatment options such as the use of Long-Acting Antipsychotics (LAI's) to minimise the risk of relapse. These attitudes mediate compromised clinical decision making that could be contributing to sub-optimal care delivery. Given the crisis in care delivery affecting psychiatric services, the study calls for education of patients, carers and staff regarding the evidence-based therapeutic options available to anticipate, manage and minimise the incidence of relapse in schizophrenia.

Keywords: Schizophrenia, Relapse, Staff Attitudes, Relapse Prevention, Non-Adherence

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I. Introduction

The King's Fund (2015) briefing reflects the extreme pressure that many mental health services are experiencing, raising issues of concern. "Bed occupancy in inpatient facilities is frequently well above recommended levels, with community services, crisis resolution, and home treatment teams, often unable to provide sufficient levels of support to compensate for reductions in beds. This is having a negative impact on safety and quality of care. The lack of available beds is leading to high numbers of out-of-area placements for inpatients. Out-of-area placements are costly, lead to increased hospitalisations, discontinuities in care and an increased risk of suicide" (King's Fund 2015). As of September 2019, the National Health Service (NHS) spent 11.3 million (NHS Digital 2019) on out-of-area placements, which, an outcomes study found, when compared to patients admitted locally, "OAPs are expensive, inefficient, distressing for patients, and may increase risk. We found that there were significantly increased lengths of stay, more subsequent contacts with services, and more self-harm in this group" (Galante et al. 2019). The study concludes that "The results were substantially worse in key respects for patients who go to OAPs, raising further questions about their quality and the economic impact to the NHS" (Galante et al. 2019).

The combination of rising demand and cutbacks in services has reinvigorated the search for cost-effective treatments in a time of austerity. The King's Fund (2015) comments that "service reconfigurations triggered by this continuing crisis has led to the adoption of policies which have little or no evidence base. These initiatives represent a leap in the dark, with little formal evaluation to indicate impact on the quality of or access to care" (). Lack of bed availability, particularly for patients in acute need, is a widely identified bottleneck in care provision (Langford 2013). Bed occupancy comes at a high cost, especially with the rising reliance on the

private sector to provide it. It is one of the biggest elements in healthcare cost of schizophrenia, so reductions in hospitalisation rates could be expected to not only help financially but would also improve the quality of service (Ascher-Svanum et al. 2010). Three evidence-based policies are associated with reduced bed occupancy: Crisis intervention and home treatment (Ratna 1992), Intensive case management (Dieterich et al. 2017) and the utilisation of long-acting antipsychotics in schizophrenia (Taipale et al. 2017). Whilst the first two options have driven national policies aimed at improving community care, the third has received less attention, despite its evidence base in real-world studies.

There is also evidence of increasing use of coercion in community care, reflected in the utilisation of involuntary admission to manage acutely disturbed and relapsing patients. There has been a 40% increase in detentions under the Mental Health Act, from 45,484 in 2005/2006 to 63,622 in 2015/16. (CQC 2016). Many of these repeat sections are often of relapsing patients' noncompliance with their medications. Because psychopathology and social functioning and, consequently, hospitalisation rates can worsen with repeated psychotic episodes in patients with schizophrenia, relapse prevention is a critical goal, not only for the patient but also for care providers, especially as the treatment of schizophrenia incurs the highest aggregate cost to provide (Cloutier et al. 2013). Costs associated with the management of relapse may account for the largest share of treatment costs in schizophrenia (Svarstad et al. 2001). A Cochrane database analysis of all randomised controlled trials (RCTs) published from 1959 to 2017 found that maintenance on antipsychotic drugs prevents relapse to a much greater extent than placebo (Ceraso et al. 2020). Dufort and Zipursky (2020) in their analysis of the literature found that the most important risk factor associated with relapse is medication nonadherence. A meta-analysis of longitudinal studies found that poor adherence was a significant factor mediating relapse (Alvarez-Jimenez et al. 2012). Additionally, there is evidence that continued adherence reduces the risk of hospitalisations in chronic and first-episode patients (Leucht et al. 2012; Tinhoen et al. 2018). Poor medication adherence, as with other medical conditions, is a public health issue in serious mental illnesses, and it is magnified by a lack of insight and cognitive deficits. Several prospective observational studies report that non-adherence was associated with a significantly higher rate of psychiatric hospitalisation, use of emergency psychiatric services, arrest, violence, victimisation, substance use, poorer mental functioning, poorer life satisfaction and more alcohol-related problems (Ascher-Svanum et al. 2006; Novick et al. 2010). Both patients and prescribers overestimate adherence rates, as shown by studies in which adherence is measured electronically (Byerly et al. 2005); improved adherence is likely to result in better clinical and patient-reported outcomes (Hayhurst et al. 2014). The development of long acting injectable antipsychotics was an attempt to deal with non-compliance, but it also may have other benefits such as stable blood levels, avoiding the peaks and troughs of oral medication (Spanarello and La Ferla 2014). There is a growing evidence base regarding their acceptability, efficacy and value in reducing hospitalisation rates in comparison to the current reliance on oral medication for relapse prevention (Mace et al. 2019)

Evidence-Based Practice

The research literature depicts an evolving picture regarding the relative merits of long-acting injectable (LAI) and oral medication in minimising the risk of relapse schizophrenia. The results vary with the research methodology utilised. There are three main classes of research methodologies that have been used: RCTs, mirror studies and cohort studies. The consensus from several large RCTs is that LAIs are comparable with but not significantly superior to oral antipsychotics (Kishimoto et al. 2014). Meta-analyses of RCTs did not find a significant difference between LAIs and OAPs in preventing relapse or hospitalisation or in secondary outcomes related to relapse. However, RCTs tend to enrol a disproportionate number of patients with better relations with treating teams, better treatment adherence and lower illness severity, all of which are associated with better outcomes. Another major issue in RCTs is the exclusion of patients with substance abuse, suicidal or antisocial behaviour or mental or physical comorbidity—features associated with increased hospitalisation rates. RCTs of their nature, therefore, exclude the type of patients that are most likely to have a relative advantage from the use of LAIs. Additionally, participation in clinical trials alters the logistics of care delivery. Consistent with requirements of the research protocol, clients receive increased levels of care input with structured appointment reminders, reimbursements and repeated symptom, social and adherence assessments; these are known to improve treatment adherence. Therefore, the standard RCT might not be the best strategy to examine the effectiveness of LAIs compared to OAPs, particularly where patients have a poor relationship with treatment services and would be unwilling to give informed consent or comply with the rigors of a research study.

The second class of studies that are closer to the real world environment are mirror studies that use the patients as their own control. A meta-analysis of mirror-image studies, in which hospitalisation risk/rate during a period of OAP treatment was compared with a subsequent period of being treated with LAIs, demonstrated significant superiority of LAIs over OAPs (Kishimoto et al. 2013). Effect sizes were large for preventing hospitalisation (risk ratio = 0.43) and decreasing the number of hospitalisations (rate ratio = 0.38). Mirror image studies have methodological problems of their own, such as expectation bias and regression to the mean.

Another group of studies that maintain real-world conditions are cohort studies; they follow-up parallel groups of patients over a defined period. A meta-analysis of 42 parallel-group nonrandomised cohort studies, comparing LAIs and OAPs for the treatment of schizophrenia, found that LAIs were superior to OAPs in decreasing the hospitalisation rate—number of hospitalisations per unit time (Kishimoto et al. 2018). Regarding secondary outcomes, however, the meta-analysis found no difference in the risk of hospitalisation (although trend-level significance was observed) and the number of hospital days. This needs to be balanced against other risk factors; the patients on LAI in these studies had clinical characteristics consistent with greater severity and chronicity than those on oral. The Finnish database study is worth noting not only because of its size (62,250 patients, which included 8,719 first episode patients) and the period of follow-up (up to 20 years), it utilised within-patient comparison markers and aimed at determining the effectiveness of antipsychotic treatments for the prevention of psychiatric rehospitalisation and treatment failure in schizophrenia. It concludes that “Clozapine and LAIs are the most effective treatments in preventing psychiatric and all-cause hospitalisation among chronic and first-episode patients with schizophrenia” (Taipale et al. 2019).

In summary, the nearer the study method approximates to the real world, the clearer is the body of evidence that LAIs when compared to OAPs are a better option in terms for reducing the reliance on hospitalisations. One important objection to LAIs that have influenced policy in cash-starved mental health trusts is the higher drug costs of the LAIs, especially the newer atypical LAIs. There have been a large number of studies using different measures to examine the pharmaco-economics of LAIs; they paint a consistent but uneven picture that the higher initial costs of the drugs are offset by reductions in bed occupation and emergency care (Lin et al. 2013; Bera et al. 2014; Baser et al. 2015). This appears to be also true for the higher costing second-generation LAIs (Pilon et al. 2019). The increased dosage intervals of the latest LAIs appear to be driving greater patient acceptability, which has been a limiting factor in the past (Blackwood et al. 2020).

Given the real-world evidence of value in reducing hospital days and costs, the question arises as to why LAIs are not a more actively explored option at a time of crisis, in terms of bed occupation and financial cutbacks. There is a body of evidence that knowledge and attitudes among clinicians, support staff and patients maybe a limiting factor. A negative attitude amongst clinicians regarding LAIs is common (Heres et al. 2006; Jaeger and Rossler 2010; Patel et al. 2010), especially when considering first-episode patients. In a survey in the United Kingdom, most psychiatrists (91%) were of the view that LAIs were as efficacious as oral, (81%) felt they improve patient adherence and (94%) thought that they prevent relapse. These beliefs, however, often do not translate into practice with in one study 50% of psychiatrists reporting a decrease in use (Patel et al. 2003). LAIs are often perceived to be stigmatising (48%), and there is a widespread (69%) but unaddressed belief that they are not acceptable to patients (Patel et al. 2010). A survey of nurses in the United Kingdom found that they were significantly more likely than the psychiatrists to characterise LAIs as “coercive, compromising of patient autonomy, or more bothersome to prescribe and monitor than oral medication” (Patel et al. 2005). Regarding patients themselves, many have a negative impression of LAIs and perceive them as more coercive (Jaeger and Rossler 2010). However, with the emergence of newer LAIs, where the interval between injections is longer, several studies are reporting more positive attitudes (Blackwood 2019; Mace et al. 2019). In Blackwood’s (2019) survey, 77% of the 1,402 participants preferred LAIs over daily pills. Regarding the cheaper traditional LAIs, as with all prejudices experience, assumptions and lack of information all play a role. Jaeger and Rossler (2010) in their survey found that “67% of all patients in our sample did not receive information about depot antipsychotics from their psychiatrist”. 75% of psychiatrists felt that they informed the patient, but only 33% of patients felt informed. With clinicians, greater knowledge of LAIs correlate with more positive attitudes (Waddell and Taylor 2009); patient responses are modulated by experience. Patients who have had the experience of being on LAIs have more favourable attitudes than those who have not (Patel et al. 2009). LAI users were more likely, than those on oral treatment, to agree that LAIs keep patients out of hospital and that the injection ensured delivery of the right amount of medication (Mace et al. 2019). It has also been shown that the manner in which patients are informed affects their acceptability of LAIs. A positivist presentation led to 96% acceptance by patients who had previously rejected the option (Weiden et al. 2015). This suggests that education of patients’ carers and clinicians is a key goal in exploring the options on offer, to maximise relapse prevention (Correll 2014).

Attitudes Survey

It, therefore, becomes clinically relevant to map the levels of information and survey the extent of the attitudes that limit the potential utilisation of evidence-based options for reducing bed occupation. This is a pilot study in a trust that has the second-highest rate of out-of-area placements (BMA 2018); it has home treatment services but no crisis service. The study differs from previous studies in that it maps the knowledge and attitudes of all classes of service providers and those of the patients they care for. All previous studies have addressed providers and patients separately.

II. Method

The study was approved by the National Institute of Health Research (IRAS: 207006). A cross-sectional survey design was utilised to assess the attitudes of health care professionals (HCPs) in Barnet Enfield and Haringey Mental Health (BEH MH) Trust. All inpatient and outpatient units (home treatment, continuing care complex care, early intervention, community support and recovery, and community rehabilitation teams) were approached by the clinical study officers of the trust, to recruit the HCPs. The inclusion criterion for the HCPs was that they should be involved in the long-term treatment of SUs with schizophrenia; they were excluded if they were unwilling to participate. The HCPs were given an information sheet about the study and if they expressed interest, they were consented to participate and were presented with the questionnaire which was estimated to last 20 minutes.

The questionnaire started with a demographic section that was tailored around their professional characteristics, as reflected in *Table 1*. Then, the HCPs were presented with a questionnaire about their attitudes and knowledge towards LAIs; it was created by the research team based on existing literature on LAIs but also the National Institute for Health and Care Excellence (NICE) (2014) guidelines on them. The main areas that the questionnaire focused on were the advantages, disadvantages and potential reasons that would make HCPs consider LAIs, as reflected in *Table 2*, HCPs had to tick the items that reflected their opinions. In addition to that, that questionnaire had items on research and the NICE guidelines around LAIs, as reflected in *Table 3*, where the clinicians needed to indicate whether they believed those statements to be “True”, “False” or “Don’t Know”.

III. Results

Professionals ($N = 80$) were recruited from all services within the BEH Trust. Majority of HCPs were recruited from inpatient units ($N = 25$, 31.3%), followed by the early intervention services ($N = 22$, 27.5%), home treatment teams ($N = 15$, 18.8%), rehab units ($N = 9$, 11.3%), community support and recovery teams ($N = 4$, 5%), wellbeing clinics ($N = 4$, 5%) and, lastly, complex care teams ($N = 1$, 1.4%). Their characteristics can be found in *Table 1* and their attitudes towards utilising LAIs can be found in *Table 2*. In addition to that, their knowledge of the NICE guidelines and research around LAIs can be found in *Table 3* and *Table 4*. Percentages in tables 3 and 4 are presented in order of “True”, “False” and “Don’t know”.

Table 1. Characteristics of the mental health professionals

Profession	Age	Gender (Males (Ma), Females (F))	Years in Practice	Patients on Caseload	Patients on LAI	Patients on LAI and CTO	Importance of Relapse Prevention for (%) of patients:
Doctors (20.8%)		M= 43.8%, F= 46.3%	$M = 16.6$, $SD = 9.2$	$M = 84.08$, $SD = 145.75$	$M = 22$, $SD = 30.94$	$M = 14.73$, $SD = 28.71$	79.46%
Psychologists / Therapists (7.8%)	$M = 33.67$, $SD = 20.56$	M= 33.3%, F= 66.7%	$M = 13.33$, $SD = 14.67$	$M = 22$, $SD = 24.36$	$M = 14.25$, $SD = 17.75$	$M = 13.5$, $SD = 24.37$	80.8%
Nurses (46.8%)	$M = 36.8$, $SD = 19$	M= 44.4%, F= 55.6%	$M = 12.74$, $SD = 8.94$	$M = 105.17$, $SD = 163.18$	$M = 27.3$, $SD = 66.44$	$M = 2.75$, $SD = 5.5$	70.38%
Social Workers (10.4%)	$M = 38.38$, $SD = 10.03$	M = 50%, F = 50%	$M = 5.5$, $SD = 3.55$	$M = 20.43$, $SD = 8.18$	$M = 5.2$, $SD = 5.85$	$M = 4.5$, $SD = 8.35$	50.33%
Support Workers / Other Staff (14.3%)	$M = 33.36$, $SD = 14.44$	M=27.3,F F= 72.7%	$M = 9.27$, $SD = 7.32$	$M = 33.67$, $SD = 19.44$	$M = 3.22$, $SD = 3.31$	$M = 1$, $SD = 1$	96.11%

Table 2. Mental Health professionals’ beliefs towards utilising LAIs

	Doctors	Psychologists / Therapists	Nurses	Social Workers	Support Workers/ Other Staff
Disadvantages					
Cost	37.5%	16.7%	44.4%	37.5%	36.4%
No better than oral	0%	0%	11.1%	0%	9.1%
Requires 2-4 weekly visits to clinic	12.5%	66.7%	61.1%	62.5%	54.5%
Patient resistance	81.3%	100%	47.2%	50%	81.8%
Drug level cannot be adjusted immediately when there are side effects	62.5%	83.3%	72.2%	50%	63.6%
LAI’s are coercive	6.3%	33.3%	11.1%	62.5%	18.2%
Takes away patients’ responsibility/ autonomy/stigmatising	43.8%	50%	50%	75%	36.4%
Intrudes on patient’s privacy	25%	83.3%	58.3%	62.5%	36.4%
Needles	75%	83.3%	72.2%	75%	72.7%
My patients are compliant with oral	0%	16.7%	2.8%	0%	9.1%

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Oral non-compliance can be detected and addressed	12.5%	16.7%	25%	12.5%	27.3%
LAI's are more bothersome to prescribe/monitor	0%	16.7%	8.3%	12.5%	9.1%
Advantages					
Certainty of drug delivery	100%	66.7%	69.4%	75%	63.6%
Simplifies and ensures consistent drug delivery in the long term	87.5%	66.7%	61.1%	87.5%	81.8%
Eliminates remembering to take tablet everyday/simplifies drug regime	93.8%	83.3%	83.3%	87.5%	100%
Avoids the need for compliance checks (questioning patients checking blister packs)	75%	66.7%	63.9%	87.5%	63.6%
Helps distinguish relapse due to treatment resistance from drug from noncompliance	87.5%	66.7%	66.7%	50%	45.5%
Detects early non-compliance when patient doesn't attend	87.5%	83.3%	72.2%	87.5%	81.8%
Regular contact with services	93.8%	83.3%	80.6%	100%	81.8%
Predictable stable plasma levels (possibility of lower dose)	62.5%	33.3%	41.7%	37.5%	18.2%
Avoids the fluctuations in drug levels that occur with oral (consistent bioavailability)	81.3%	50%	41.7%	50%	45.5%
Symptoms which would make me consider a depot are:					
Lack of insight	75%	50%	52.8%	50%	36.4%
Negative symptoms (apathy, lack of drive, poor self-care)	25%	33.3%	36.1%	50%	0%
Drug use	37.5%	16.7%	19.4%	25%	18.2%
Disorganised lifestyle	87.5%	66.7%	36.1%	87.5%	54.5%
Patient resistance to medications	68.8%	66.7%	63.9%	62.5%	54.5%
Cognitive symptoms (lack of planning, executive dysfunction)	43.8%	50%	30.6%	37.5%	27.3%
Negative attitudes to care services	43.8%	16.7%	33.3%	37.5%	0%
History of non-compliance	100%	83.3%	88.9%	87.5%	90.9%
History of relapse	81.3%	83.3%	86.1%	100%	63.6%
Living alone/ lack of carer/lack of support	56.3%	50%	44.4%	62.5%	27.3%
Unstable living conditions	75%	66.7%	27.8%	25%	27.3%
History of violence	62.5%	50%	19.4%	25%	27.3%

Chi Square Tests

Furthermore, chi-squared tests for independence were performed to further explore the differences between the attitudes of the (health care assistants) HCAs. The following relationships of statistical significance have come up:

- A significant association between the professional status and considering “depot requires 2–4 weekly visits to clinic” as a disadvantage, $\chi^2(4, N = 77) = 12.02, p = .017, \phi = .395$. Specifically, doctors were more likely to not tick that box in comparison to psychologists/therapists, nurses, social workers and support workers/other staff who were more likely to tick that box.
- A significant association between the professional status and considering “patient resistance” as a disadvantage for depot, $\chi^2(4, N = 77) = 12, p = .018, \phi = .394$. Specifically, nurses were more likely to not tick that box in comparison to psychologists/therapists, doctors and support workers/other staff who were more likely to tick that box. Support workers were equally distributed between the two groups.
- A significant association between the professional status and considering “LAIs are coercive” as a disadvantage for depot, $\chi^2(4, N = 77) = 14.23, p = .007, \phi = .430$. Specifically, nurses, doctors, psychologists/therapists and support workers/other staff were more likely to not tick that box in comparison to social workers that were most likely to tick the box.
- A significant association between the professional status and considering “disorganised lifestyle” as an indicator for depot, $\chi^2(4, N = 77) = 15.79, p = .003, \phi = .453$. Specifically, doctors, psychologists/therapists, social workers and support workers/other staff were more likely to tick that box in comparison to nurses who were more likely to not tick that box.
- A significant association between the professional status and considering “unstable living conditions” as an indicator for depot, $\chi^2(4, N = 77) = 13.65, p = .009, \phi = .421$. Specifically, doctors and psychologists/therapists were more likely to tick that box in comparison to nurses, social workers and support workers/other staff who were more likely to not tick that box.
- A significant association between the professional status and considering “history of violence” as an indicator for depot, $\chi^2(4, N = 77) = 10.55, p = .032, \phi = .370$. Specifically, doctors were more likely to tick that box in comparison to nurses, social workers and support workers/other staff who were more likely to not tick that box. Psychologists/therapists were equally distributed between the two groups.

- A significant association between the professional status and knowledge of research regarding LAI therapy being more expensive than the oral counterpart, $\chi^2(8, N = 70) = 23.47, p = .003, \phi = .579$. Specifically, doctors were more likely to tick “Don’t know” while psychologists/therapists and social workers were equally distributed between “True” and “False”. Nurses were more likely to tick “True” and support workers/other staff were more likely to tick “False”.

Table 3. Knowledge of NICE guidelines around LAIs

	Doctors	Psychologists / Therapists	Nurses	Social Workers	Support Workers / Other Staff
<u>The (2014) guidelines recommend that LAIs (True/ False/ Don't Know):</u>					
Be prescribed to patients with an observed history of noncompliance leading to relapses	81.3 %, 12.5%, 6.3 %	66.7%, 0%, 33.3%	58.3%, 5.6%, 36.1%	62.5%, 0%, 37.5%	63.6%, 0%, 36.3%
Be offered to all patients after an episode	43.8%, 56.3%, 0%	0%, 50%, 50%	19.4%, 35.5%, 45.2%	12.5%, 50%, 37.5%	9.1%, 45.5%, 45.5%
To be avoided in first episode patients	56.3%, 37.5%, 6.3%	60%, 0%, 40%	41.9%, 22.6%, 35.5%	62.5%, 25%, 12.5%	36.4%, 18.2%, 45.5%
To be considered where overt or covert noncompliance needs to be avoided	75%, 6.3%, 18.8%	33.3%, 0%, 66.7%	51.6%, 0%, 48.4%	42.9%, 13.3%, 42.9%	45.5%, 0%, 54.5%

Table 4. Knowledge of Research around LAIs(True/ False/ Don't Know):

	Doctors	Psychologists / Therapists	Nurses	Social Workers	Support Workers / Other Staff
<u>Research (True/ False/ Don't know)</u>					
Randomised controlled consistently trials show that patients on oral maintenance have fewer relapses than patients on Long-acting injections	6.3%, 68.8%, 25%	16.7%, 33.3%, 50%	16.7%, 33.3%, 50%	12.5%, 25%, 62.5%	9.1%, 36.4%, 54.5%
Cost benefit analyses of oral vs. LAI maintenance therapy show that LAI patients are more expensive	18.8%, 62.5%, 18.8%	50%, 0%, 50%	20.7%, 17.2%, 62%	50%, 0%, 50%	54.5%, 9.1%, 36.4%
Mirror image studies comparing the period before LAI's to after showed no differences the number of hospitalisations	6.3%, 56.3%, 37.5%	16.7%, 16.7%, 66.7%	16.7%, 20%, 63.3%	0%, 14.3%, 85.7%	18.2%, 27.3%, 54.5%
Large database studies of all patients show no differences in the number of hospitalisations of patients on oral compared to LAI	31.3%, 50%, 18.8%	16.7%, 16.7%, 66.7%	12.9%, 29%, 58.1%	12.5%, 25%, 62.5%	18.2%, 9.1%, 72.2%

IV. Discussion

To our knowledge, this is the first survey study of all classes of staff, in all settings and the patients they care for. All previous studies have dealt with the elements in separate groupings and not included all the different members of the treating team. These findings indicate widespread knowledge deficits associated with negative cognitive constructs about potentially helpful treatment options, which are likely to be affecting key treatment decisions. There appears to be a lack of awareness of the seriousness of relapse in schizophrenia, not just for the patient but also for the services. The clinical awareness that relapse prevention is a key target in the management of a recurring illness is not universal. Awareness was highest amongst support workers (96%) and lowest in social workers (50%). Doctors show high levels of knowledge and positive attitudes to LAI. Under current practice patterns, however, their role has fallen to a handful of reviews a year. All the other staff, who are involved in day-to-day management of the patients, have high levels of knowledge deficits, which is associated with negative attitudes, especially highest among social workers and psychologists. Whilst the antipathy of therapists to drugs as a core element of the treatment plan is understandable, the negative attitudes of the social workers who bear the brunt of mental health act assessments and the travail of searching for beds is not. This suggests a disconnection between the clinical challenges being acutely experienced and the need to explore possible solutions, especially with repeated relapses due to noncompliance. Part 2 of Table 3 “Symptoms which would make me consider a depot” was devised to elicit clinical awareness of research-based markers of potential non-compliance. The responses indicate that awareness of these antecedents of relapse was patchy and uneven across the clinical spectrum of care providers. This is in accord with other studies reporting that there is only a limited awareness of the evidence-based markers of noncompliance (Lacro et al. 2002). Drug abuse, one of the most consistent markers, was not rated as a risk factor by most staff (Schoeler et al. 2017). The range of responses regarding it as a risk was from a high of 37% of doctors to as low as 16% among

psychologists. As shown in other studies, staff tended to continue to rely on OAPs even when non-compliance was manifest, with over a third of all staff not listing the possible use of LAIs as an alternative option. Many of the patients were placed on enhanced CPA, but the efforts to deploy known strategies to address non-compliance were patchy and inconsistent (Haddad et al. 2014). When patients were repeatedly hospitalised, LAIs were more actively offered, but often, it was in the coercive context of a CTO (Lambert et al. 2009). One British study found that hospital use and costs were higher when patients were placed on LAIs (Young and Taylor 2006). Most of the patients in this study were placed on LAIs when they were inpatients, often on a section. Whilst this conclusion is an outlier contradicted by other studies, indicating cost savings or neutrality, it does indicate the need to anticipate the risk of relapse and make a more orderly patient inclusive transition, as envisioned by the NICE guidelines, to achieve optimal outcomes. Interestingly, the belief that LAIs were coercive, which was listed as a significant driver of non-use in many other studies, was not validated in this study; only 6.3% of doctors and 11% of nurses regarded them as coercive. It is social workers who saw them as such (61%). This may be due to the fact that the trust has a set of well-organised wellbeing services that cater for patients on LAIs or clozapine.

A disorganised lifestyle was regarded by all classes of treatment providers as a risk for non-compliance, but one of its associated/causative agents—impaired cognition—was responded as less so. This suggests that it was mainly as a social issue rather than potentially a neurocognitive illness issue. In general, the awareness of cognitive symptoms and their consequences in treatment compliance was low (Green et al. 2000). Nuechterleinet et al. (2020) found that cognitive remediation combined with LAIs can significantly improve core cognitive deficits in this difficult group.

Markers of manifest non-compliance, such as repeated relapses and negative relationships with treatment teams, were acknowledged by all the treatment teams as a risk factor that would favour the use of LAIs. The clinical problem in relapse on oral medication is that it is unclear whether the relapse was mediated by drug failure or non-compliance. Clinically, increases in dose or drug switches are often triggered to resolve the episode. One of the reasons why, in the Finnish study of first-episode, psychotics placed on LAIs spent up to 30% less time in hospitals was maybe because it neutralised the clinical uncertainty regarding non-compliance, permitting more informed drug switches when needed (Tinhoen et al. 2011).

This survey of attitudes reflects and elaborates on previous studies that showed deficits in knowledge and attitudes regarding options for minimising relapse, by ensuring compliance with treatment. Given that schizophrenia is known to be a relapsing illness, this lack of a treatment planning focus on the trajectory of the illness is clinically counter-productive. Consistent with this attitude, there were deficits in knowledge about the role of non-compliance and factors associated with it, such as drug abuse. A variety of risk assessments are regularly carried out in care planning, but the risk of non-compliance and relapse is not systematically addressed through the monitoring of recognised markers (Lacro et al. 2002). This is reflected in the responses to the items in *Table 3*. The thrust of therapy appears to be primarily existential—the focus being on maximising symptom control in the current context of treatment before transferring the patient to the next link in the service chain—from in-patient to community treatment and from community to the GP. There was little evidence of long-term planning and analysis of the evolving risk of relapse over time. Whilst there were adequate plans to manage relapse once the signs became manifest, through the use of crisis plans, few clinical resources of the treating team appear to be allotted to relapse anticipation and proactive prevention (Haddad et al. 2014).

Regarding the knowledge base, there were significant variations in the level of knowledge. Doctors had the highest levels but appeared unsure ticking the “*don't know*” on many issues (*Table 4*). There appear to be limitations in the knowledge of the NICE guidelines, especially on discussing treatment options after an episode of relapse. As in previous studies, team members at all levels had negative attitudes towards the value of LAIs in the first episode, 56% of doctors stating it to be false. The greatest evidence of knowledge deficits is in the awareness of research and its clinical implications. *Table 4* reflects a worrying lack of awareness of evolving research and the benefits it may offer to patients. The medical staff who had shown the most knowledge on the other items responded with “*don't know*” or were in error up to 50% of the time. All other groups of staff were unaware of the different types of research evidence, with “*don't know*” dominating the responses. The greatest lack of awareness was in the conclusions of real-world studies. Whilst there was a commitment to evidence-based treatments, there is a knowledge gap in the evolution of the research findings and the tendency to apply research findings to patients who were excluded from the research studies relied upon to form the clinical judgement.

Limitations: The study sample needs to be larger, and the study needs to be replicated in other trusts, to exclude local factors that may have affected the views expressed. On the other hand, the trust functions as three separate sectors and all the staff specialties were successfully recruited. The scales used are not standardised; there are no standardised assessment scales for measuring staff attitudes. The scales that were used were developed through discussions with staff and patients in services all over the country. They echo the data explored in other surveys of attitudes in the published literature. By recruiting all classes of professionals from a single trust, this study minimises nosocomial factors.

V. Summary and Conclusions

The findings of this study show that there is evidence of knowledge deficits and attitudinal issues that may be affecting the delivery of optimal long-term care to schizophrenic patients. Psychoeducation of both patients and providers appears to be called for. There are some indications that there is a lack of awareness of the seriousness of relapse in the life of the patient and the consequent impact relapses have on service delivery. Non-adherence in patients with schizophrenia is common and difficult to detect and manage. Although LAIs may provide one method to help improve treatment adherence, only a minority of medication non-adherent patients receive them. The use of CTOs to deliver LAIs needs to be reviewed. The gulf between the conclusions of real-world studies when compared to RCTs raises questions about the excessive reliance on RCTs as a key driver of clinical policy when treating non-adherent challenging patients who were excluded from these studies.

References

- [1]. Alvarez-Jimenez, M., A. Priede, S. E. Hetrick, S. Bendall, E. Killackey, A. G. Parker, P. D. McGorry and J. F. Gleeson. 2012. "Risk Factors for Relapse Following Treatment for First Episode Psychosis: A Systematic Review and Meta-Analysis of Longitudinal Studies." *Schizophrenia Research* 139, no. 1–3: 116–128. doi:10.1016/j.schres.2012.05.007, PubMed: 22658527.
- [2]. Andreasen, Nancy C., William T. Carpenter Jr., John M. Kane, Robert A. Lasser, Stephen R. Marder and Daniel R. Weinberger. 2005. "Remission in Schizophrenia: Proposed Criteria and Rationale for Consensus." *American Journal of Psychiatry* 162, no. 3: 441–449. doi: 10.1176/appi.ajp.162.3.441, PubMed: 15741458.
- [3]. Ascher-Svanum, Haya, Douglas E. Faries, Baojin Zhu, Frank R. Ernst, Marvin S. Swartz and Jeff W. Swanson. 2006. "Medication Adherence and Long-Term Functional Outcomes in the Treatment of Schizophrenia in Usual Care." *Journal of Clinical Psychiatry* 67, no. 3: 453–460. doi: 10.4088/jcp.v67n0317, PubMed: 16649833.
- [4]. Ascher-Svanum, Haya, Baojin Zhu, Douglas E. Faries, David Salkever, Eric P. Slade, Xiaomei Peng and Robert R. Conley. 2010. "The Cost of Relapse and the Predictors of Relapse in the Treatment of Schizophrenia." *BMC Psychiatry* 10: 2. doi: 10.1186/1471-244X-10-2, PubMed: 20059765.
- [5]. Baser, Onur, Lin Xie, Jacqueline Pesa and Mike Durkin. 2015. "Healthcare Utilization and Costs of Veterans Health Administration Patients with Schizophrenia Treated with Paliperidone Palmitate Long-Acting Injection or Oral Atypical Antipsychotics." *Journal of Medical Economics* 18, no. 5: 357–365. doi: 10.3111/13696998.2014.1001514, PubMed: 25525771.
- [6]. Bera, Rimal, Steve Offord, Donna Zubek, Gina Lau, Jay Lin and Craig Karson. 2014. "Hospitalization Resource Utilization and Costs Among Medicaid Insured Patients with Schizophrenia with Different Treatment Durations of Long-Acting Injectable Antipsychotic Therapy." *Journal of Clinical Psychopharmacology* 34, no. 1: 30–35. doi: 10.1097/JCP.0b013e3182a6082a, PubMed: 24135840.
- [7]. Blackwood, Clifton, Panna Sanga, Isaac Nuamah, Alexander Keenan, Arun Singh, Maju Mathews and Srihari Gopal. 2020. "Patients' Preference for Long-Acting Injectable Versus Oral Antipsychotics in Schizophrenia: Results from the Patient-Reported Medication Preference Questionnaire." *Patient Prefer Adherence* 14: 1093–1102. doi: 10.2147/PPA.S251812, PubMed: 32753849.
- [8]. BMA. n.d. Accessed May 6, 2021. <https://www.bma.org.uk/news/media-centre/press-releases/2017/june/bma-figures-show-stellar-rise-in-mental-health-out-of-area-placements>, 2018
- [9]. Byerly, Matthew, Robert Fisher, Katrina Whatley, Rhiannon Holland, Femina Varghese, Thomas Carmody, Brianne Magouirk and A. John Rush. 2005. "A Comparison of Electronic Monitoring vs Clinician Rating of Antipsychotic Adherence in Outpatients with Schizophrenia." *Psychiatry Research* 133, no. 2–3: 129–133. doi: 10.1016/j.psychres.2004.11.002, PubMed: 15740989.
- [10]. Care Quality Commission. "Ongoing Rise in Detentions Under Mental Health Act May Be Symptomatic of a System 'Under Considerable Strain.'" Accessed May 6, 2021. <http://www.cqc.org.uk/news/releases/rise-mha-detentions-act-may-be-symptomatic-system-under-pressure>, 2018.
- [11]. Ceraso, Anna, Jessie Jingxia Lin, Johannes Schneider-Thoma, Spyridon Sifafis, Magdolna Tardy, Katja Komossa, Stephan Heres, Werner Kissling, John M. Davis and Stefan Leucht. 2020. "Maintenance Treatment with Antipsychotic Drugs for Schizophrenia." *Cochrane Database of Systematic Reviews* 8: CD008016. doi: 10.1002/14651858.CD008016.pub3, PubMed: 32840872.
- [12]. Cloutier, Martin, Myrlene Sanon Aigbogun, Annie Guerin, Roy Nitulescu, Agnihotram V. Ramanakumar, Siddhesh A. Kamat, Michael DeLucia, Ruth Duffy, Susan N. Legacy, Crystal Henderson, Clement Francois and Eric Wu. 2016. "The Economic Burden of Schizophrenia in the United States in 2013." *Journal of Clinical Psychiatry* 77, no. 6: 764–771. doi: 10.4088/JCP.15m10278, PubMed: 27135986.
- [13]. Correll, C. U. 2014. "The Role of the Extended Health Care Team in Successful LAI Therapy: Education to Overcome Barriers." *Journal of Clinical Psychiatry* 75, no. 9: e25. doi: 10.4088/JCP.13024tx4c.
- [14]. Correll, Christoph U., Leslie Citrome, Peter M. Haddad, John Lauriello, Mark Olfson, Stephen M. Calloway and John M. Kane. 2016. "The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence." *Journal of Clinical Psychiatry* 77, no. suppl 3 [Suppl.]: 1–24. doi: 10.4088/JCP.15032su1, PubMed: 27732772.
- [15]. Dieterich, M., C. B. Irving, H. Bergman, M. A. Khokhar, B. Park and M. Marshall. 2017. "Intensive Case Management for Severe Mental Illness." *Cochrane Database of Systematic Reviews* 1, no. 10. CD007906.pub. 3. doi: 10.1002/14651858.CD007906.pub3, PubMed Central: 6472672, PubMed: 28067944.
- [16]. Dufort, Alexander and Robert B. Zipursky. 2019 Jan. 3. "Understanding and Managing Treatment Adherence in Schizophrenia." *Clinical Schizophrenia & Related Psychoses*. doi: 10.3371/CSRP.ADRZ.121218 [Epub ahead of print]. PubMed: 30605043.
- [17]. Galante, J. R., R. Humphreys and A. Molodynski. 2019. "Out-of-Area Placements in Acute Mental Health Care: the Outcomes." *Progress in Neurology & Psychiatry* 23, no. 1: 28–30. <https://www.progressnp.com/article/out-of-area-placements-in-acute-mental-health-care-the-outcomes/>. doi: 10.1002/pnp.528.
- [18]. Green, M. F., R. S. Kern, D. L. Braff and J. Mintz. 2000. "Neurocognitive Deficits and Functional Outcome in Schizophrenia: Are We Measuring the "Right Stuff"?" *Schizophrenia Bulletin* 26, no. 1: 119–136. doi: 10.1093/oxfordjournals.schbul.a033430, PubMed: 10755673.
- [19]. Haddad, Peter M., Cecilia Brain and Jan Scott. 2014. "Nonadherence with Antipsychotic Medication in Schizophrenia: Challenges and Management Strategies." *Patient Related Outcome Measures* 5: 43–62. doi: 10.2147/PROM.S42735, PubMed: 25061342.

- [20]. Hayhurst, K. P., R. J. Drake, J. A. Massie, G. Dunn, T. R. Barnes, P. B. Jones and S. W. Lewis. 2014. "Improved Quality of Life Over One Year Is Associated with Improved Adherence in Patients with Schizophrenia." *European Psychiatry* 29, no. 3: 191–196. doi: 10.1016/j.eurpsy.2013.03.002, PubMed: 23769325.
- [21]. Heres, Stephan, Johannes Hamann, Werner Kissling and Stefan Leucht. 2006. "Attitudes of Psychiatrists Toward Antipsychotic Depot Medication." *Journal of Clinical Psychiatry* 67, no. 12: 1948–1953. doi: 10.4088/jcp.v67n1216, PubMed: 17194274.
- [22]. Jaeger, M. and W. Rossler. 2010. "Attitudes Towards Long-Acting Depot Antipsychotics: a Survey of Patients, Relatives and Psychiatrists." *Psychiatry Research* Jan 30, no. 175(1–2):58–62. doi: 10.1016/j.psychres.2008.11.003
- [23]. King's Fund. 2015. "Mental Health Services Under Pressure." Briefing. Accessed May 6, 2021. <https://www.kingsfund.org.uk/publications/mental-health-under-pressure>, 2015.
- [24]. Kishimoto, Taishiro, Katsuhiko Hagi, Masahiro Nitta, Stefan Leucht, Mark Olfson, John M. Kane and Christoph U. Correll. 2018. "Effectiveness of Long-Acting Injectable vs Oral Antipsychotics in Patients with Schizophrenia: A Meta-Analysis of Prospective and Retrospective Cohort Studies." *Schizophrenia Bulletin* 44, no. 3: 603–619. doi: 10.1093/schbul/sbx090, PubMed: 29868849.
- [25]. Kishimoto, Taishiro, Masahiro Nitta, Michael Borenstein, John M. Kane and Christoph U. Correll. 2013. "Long-Acting Injectable Versus Oral Antipsychotics in Schizophrenia: a Systematic Review and Meta-Analysis of Mirror-Image Studies." *Journal of Clinical Psychiatry* 74, no. 10: 957–965. doi: 10.4088/JCP.13r08440, PubMed: 24229745.
- [26]. Lacro, Jonathan P., Laura B. Dunn, Christian R. Dolder, Susan G. Leckband and Dilip V. Jeste. 2002. "Prevalence of and Risk Factors for Medication Nonadherence in Patients with Schizophrenia: a Comprehensive Review of Recent Literature." *Journal of Clinical Psychiatry* 63, no. 10: 892–909. doi: 10.4088/jcp.v63n1007, PubMed: 12416599.
- [27]. Lambert, Tim J., Bruce S. Singh and Maxine N. Patel. 2009. "Community Treatment Orders and Antipsychotic Long-Acting Injections." *British Journal of Psychiatry. Supplement* 52, no. v: S57–S62. doi: 10.1192/bjp.195.52.s57, PubMed: 19880919.
- [28]. Langford, A. n.d. "Why Mental Health Bed Cuts Make Me Ashamed to Work for the NHS." Accessed May 6, 2021. <https://www.theguardian.com/society/2013/oct/23/mental-health-bed-cuts-ashamed-nhs>
- [29]. Lieberman, Jeffrey A., T. Scott Stroup, Joseph P. McEvoy, Marvin S. Swartz, Robert A. Rosenheck, Diana O. Perkins, Richard S. E. Keefe, Sonia M. Davis, Clarence E. Davis, Barry D. Lebowitz, Joanne Severe, John K. "Hsiao and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. 2005. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia." *New England Journal of Medicine* 353, no. 12: 1209–1223. doi: 10.1056/NEJMoa051688, PubMed: 16172203.
- [30]. Lin, Jay, Bruce Wong, Steve Offord and Dario Mirski. 2013. "Healthcare Cost Reductions Associated with the Use of LAI Formulations of Antipsychotic Medications Versus Oral Among Patients with Schizophrenia." *Journal of Behavioral Health Services & Research* 40, no. 3: 355–366. doi: 10.1007/s11414-013-9329-z, PubMed: 23579871.
- [31]. Llorca, Pierre Michel, Mocerane Abbar, Philippe Courtet, Sebastien Guillaume, Sylvie Lancrenon and Ludovic Samalin. 2013. "Guidelines for the Use and Management of Long-Acting Injectable Antipsychotics in Serious Mental Illness." *BMC Psychiatry* 13: article 340. doi: 10.1186/1471-244X-13-340, PubMed: 24359031.
- [32]. Mace, Shubhra, Oscar Chak, Sharanjeet Punny, Daniel Sedough-Abbasian, Chirag Vegad and David M. Taylor. 2019. "Positive Views on Antipsychotic Long-Acting Injections: Results of a Survey of Community Patients Prescribed Antipsychotics." *Therapeutic Advances in Psychopharmacology* 9: 2045125319860977. doi: 10.1177/2045125319860977, PubMed: 31321027.
- [33]. McCrone, P., S. Dhanasiri, A. Patel and M. Knapp, 2008. "PAYING THE PRICE: the Cost of Mental Health Care in England to." Accessed May 6, 2021. https://www.kingsfund.org.uk/sites/default/files/Paying-the-Price-the-cost-of-mental-health-care-England-2026-McCrone-Dhanasiri-Patel-Knapp-Lawton-Smith-Kings-Fund-May-2008_0.pdf vol. 2026.
- [34]. NHS. Digital. "Out of Area Placements in Mental Health Services in September 2019." Accessed May 6, 2021. <https://files.digital.nhs.uk/E7/0FDA45/oaps-rep-sep-2019.pdf>, 2019.
- [35]. Novick, Diego, Josep Maria Haro, David Suarez, Victor Perez, Ralf W. Dittmann and Peter M. Haddad. 2010. "Predictors and Clinical Consequences of Non-Adherence with Antipsychotic Medication in the Outpatient Treatment of Schizophrenia." *Psychiatry Research* 176, no. 2–3: 109–113. doi: 10.1016/j.psychres.2009.05.004, PubMed: 20185182.
- [36]. Nuechterlein, Keith H., Joseph Ventura, Kenneth L. Subotnik, Denise Gretchen-Doorly, Luana R. Turner, Laurie R. Casaus, John Luo et al. 2020. "A Randomized Controlled Trial of Cognitive Remediation and Long-Acting Injectable Risperidone After a First Episode of Schizophrenia: Improving Cognition and Work/School Functioning." *Psychological Medicine*: 1–10.
- [37]. Parellada, Eduard and Miquel Bioque. 2016. "Barriers to the Use of Long-Acting Injectable Antipsychotics in the Management of Schizophrenia." *CNS Drugs* 30, no. 8: 689–701. doi: 10.1007/s40263-016-0350-7, PubMed: 27255405.
- [38]. Patel, M. X., N. de Zoysa, M. Bernadt, J. Bindman and A. S. David. 2010. "Are Depot Antipsychotics Coercive than Tablets? The Patient's Perspective." *Journal of Psychopharmacology* 24, no. 10: 1483–1489. doi: 10.1177/0269881109103133, PubMed: 19304865.
- [39]. Patel, M. X., N. de Zoysa, M. Bernadt and A. David. 2009. "Depot and Oral Antipsychotics: Patient Preferences and Attitudes Are Not the Same Thing." *Journal of Psychopharmacology* 23, no. 7: 789–796. doi: 10.1177/0269881108092124, PubMed: 18583438.
- [40]. Patel, M. X., P. M. Haddad, I. B. Chaudhry, S. McLoughlin, N. Husain and A. S. David. 2010. "Psychiatrists' Use, Knowledge and Attitudes to First- and Second-Generation Antipsychotic Long-Acting Injections: Comparisons Over 5 Years." *Journal of Psychopharmacology* Oct 24, no. 10: 1473–1482. doi: 10.1177/0269881109104882, Epub May 28 2009. PubMed: 19477883.
- [41]. Patel, M. X., N. DE Zoysa, D. Baker and A. S. David. 2005. "Antipsychotic Depot Medication and Attitudes of Community Psychiatric Nurses." *Journal of Psychiatric & Mental Health Nursing* 12, no. 2: 237–244. doi: 10.1111/j.1365-2850.2004.00826.x, PubMed: 15788043.
- [42]. Patel, M. X., V. Nikolaou and A. S. David. 2003. "Psychiatrists' Attitude to Maintenance Medication for Patients with Schizophrenia." *Psychological Medicine* 33, no. 1: 83–89. doi: 10.1017/s0033291702006797, PubMed: 12537039.
- [43]. Perkins, Diana O. 2002. "Predictors of Noncompliance in Patients with Schizophrenia." *Journal of Clinical Psychiatry* 63, no. 12: 1121–1128. doi: 10.4088/jcp.v63n1206, PubMed: 12523871.
- [44]. Pilon, Dominic, Neeta Tandon, Marie-Hélène Lafeuille, Rhiannon Kamstra, Bruno Emond, Patrick Lefebvre and Kruti Joshi. 2017. "Treatment Patterns, Health Care Resource Utilization, and Spending in Medicaid Beneficiaries Initiating Second-Generation Long-Acting Injectable Agents Versus Oral Atypical Antipsychotics." *Clinical Therapeutics* 39, no. 10: 1972–1985.e2. doi: 10.1016/j.clinthera.2017.08.008, PubMed: 28919292.
- [45]. Ratna, L., 1992. *Recent Advances in Crisis Intervention. Volume One*, edited by Dr. N. Rao Punukollu. Huddersfield: International Institute of Crisis Intervention and Community Psychiatry.
- [46]. Schoeler, Tabea, Natalia Petros, Marta Di Forti, Ewa Klamerus, Enrico Foglia, Robin Murray and Sagnik Bhattacharyya. 2017. "Poor Medication Adherence and Risk of Relapse Associated with Continued Cannabis Use in Patients with First-Episode Psychosis: a Prospective Analysis." *Lancet Psychiatry* 4, no. 8: 627–633. doi: 10.1016/S2215-0366(17)30233-X, PubMed: 28705600.

- [47]. Spanarello, Stefano and Teresa La Ferla. 2014. "The Pharmacokinetics of Long-Acting Antipsychotic Medications." *Current Clinical Pharmacology* 9, no. 3: 310–317. doi: 10.2174/15748847113089990051, PubMed: 23343447.
- [48]. Svarstad, B. L., T. I. Shireman and J. K. Sweeney. 2001. "Using Drug Claims Data to Assess the Relationship of Medication Adherence with Hospitalization and Costs." *Psychiatric Services* 52, no. 6: 805–811. doi: 10.1176/appi.ps.52.6.805, PubMed: 11376229.
- [49]. Taipale, Heidi, JuhaMehtälä, Antti Tanskanen and JariTiihonen. 2018. "Comparative Effectiveness of Antipsychotic Drugs for Rehospitalization in Schizophrenia-A Nationwide Study with 20-Year Follow-Up." *Schizophrenia Bulletin* Oct 44, no. 6: 1381–1387. DOI: 10.1093/schbul/sbx176.PMCID, PubMed Central: 6192491. PubMed: 29272458.
- [50]. Taylor, David. 2009. "Psychopharmacology and Adverse Effects of Antipsychotic Long-Acting Injections: A Review." *British Journal of Psychiatry. Supplement* 52, no. v: S13–S19. doi: 10.1192/bjp.195.52.s13, PubMed: 19880912.
- [51]. Tiihonen, Jari, JariHaukka, Mark Taylor, Peter M. Haddad, Maxine X. Patel and Pasi Korhonen. 2011. "A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia." *American Journal of Psychiatry* 168, no. 6: 603–609. doi: 10.1176/appi.ajp.2011.10081224, PubMed: 21362741.
- [52]. Tiihonen, Jari, Antti Tanskanen and Heidi Taipale. 2018. "20-Year Nationwide Follow-Up Study on Discontinuation of Antipsychotic Treatment in First-Episode Schizophrenia." *American Journal of Psychiatry* 175, no. 8: 765–773. doi: 10.1176/appi.ajp.2018.17091001.
- [53]. Waddell, Linda and Mark Taylor. 2009. "Attitudes of Patients and Mental Health Staff to Antipsychotic Long-Acting Injections: Systematic Review." *British Journal of Psychiatry. Supplement* 52(Suppl. 52): S43–S50. doi: 10.1192/bjp.195.52.s43, PubMed: 19880916.
- [54]. Weiden, Peter J., Rebecca S. Roma, Dawn I. Velligan, Larry Alphas, Matthew DiChiara and Brad Davidson. 2015. "The Challenge of Offering Long-Acting Antipsychotic Therapies: a Preliminary Discourse Analysis of Psychiatrist Recommendations for Injectable Therapy to Patients with Schizophrenia." *Journal of Clinical Psychiatry* 76, no. 6: 684–690. doi: 10.4088/JCP.13m08946, PubMed: 25939027.
- [55]. Young, C. L. and D. M. Taylor. 2006. "Health Resource Utilization Associated with Switching to Risperidone Long-Acting Injection." *Acta Psychiatrica Scandinavica* 114, no. 1: 14–20. doi: 10.1111/j.1600-0447.2006.00766.x, PubMed: 16774656.
- [56]. Zipursky, Robert B., Natasja M. Menezes and David L. Streiner. 2014. "Risk of Symptom Recurrence with Medication Discontinuation in First-Episode Psychosis: A Systematic Review." *Schizophrenia Research* 152, no. 2–3: 408–414. doi: 10.1016/j.schres.2013.08.001, PubMed: 23972821.