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LONG-ACTING INJECTABLE (DEPOT) ANTIPSYCHOTICS AND CHANGING TREATMENT PHILOSOPHY: POSSIBLE CONTRIBUTION TO INTEGRATIVE CARE AND PERSONAL RECOVERY OF SCHIZOPHRENIA

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The field of schizophrenia drug treatment is fraught with debate, controversies and confusion. Depot or long-acting injectable antipsychotics (LAIAs) strategy in relapse prevention is not an exemption (see Kane et al. 2013). Antipsychotics are the mainstay of the successful long term treatment of patients with schizophrenia. There are four main reasons to initiate antipsychotic drug treatment: 1. to treat the presenting psychotic symptoms; 2. to prevent relapse; 3. to delay or prevent the florid onset of schizophrenia or psychotic disorder, and 4. to intervene as soon as schizophrenia or psychosis develops, in order to improve the overall outcome. Bringing the prodromal or acute phase of schizophrenia into remission as soon as possible and preventing the relapse is crucial to obtain personal recovery and maintain well-being for patients and their families. The advent of a significant number of effective and well tolerated antipsychotic drugs has increased our possibilities to treat schizophrenia and other delusional disorders in more successful ways with much better treatment outcome including full recovery. However, in clinical practice there is a huge gap between possibilities for achieving high treatment effectiveness and poor results in reality. One of the major reasons is the non-adherence to drug treatment which continues to be a significant problem and high costly issue, with all three generations of antipsychotic medications. LAIAs were developed in order to improve treatment adherence and possibly prevent relapse in patients with schizophrenia. Non-adherence to oral antipsychotics has been usually met with the so-called "difficult" medication patients including the lack of insight patients, the minimal contact patients, the negative drug attitude patients, the patients preoccupied with side-effects and negative expectations from drug treatment, the suspicious and paranoid patients, the patients who need to be in charge, the misinformation overloaded patients, the nocebo responders, etc. (see Doran 2003, Haddad et al. 2014, Jakovljevic 2014). Stigma, lack of information, fear of dependency, mental disorganization, cognitive dysfunctions, fear of liability, inadequate insurance coverage, lack of nursing support, lack of awareness are frequent causes of partial or full non-adherence. Intentional non-adherence occurs when patients make a deliberate decision not to take medications as prescribed because of real or perceived disadvantages of medications whereas non-intentional non-adherence occurs when practical problems interfere with adherence including the patient forgetting to take medication, not understanding the instructions, or having difficulty to go for prescriptions, etc. (Haddad et al. 2014).

The rates of LAIAs utilization are low and vary from 12% to 20% in the United States and Germany to 50% in Austria and Sweden (see Getzen et al. 2013). Despite the availability of a quite number of LAIAs, they are underutilized in many of the Danubian countries. For example, in Croatia where six LAIAs have been approved for use, three first-generation (FG) LAIAs (fluphenazine, haloperidol and zuclopentixol) and three second generation (SG) LAIAs (risperidon, olanzapine and paliperidone), only 11.3% patients have been on LAIAs compared to 88.7% on oral antipsychotics (IMS data, September 2014). As we have sufficient experience with LAIAs since 1966, it is timely to reconsider the treatment strategy in the maintenance treatment and relapse prevention of schizophrenia.

The advantages and limitations of LAI-As: The challenge of individualized and person-centered treatment of schizophrenia

The majority of patients with schizophrenia who are rehospitalized due to relapse are intentionally or unintentionally non-adherent, completely or in some degree. After antipsyhotic drug discontinuation, the risk of relapse increases 5-fold (Kane & Garsia-Ribera 2009, Getzen et al. 2013). According to systematic reviews between 40% and 60% patients with schizophrenia are partially or completely non-adherent with their oral antipsychotic regimes (Getzen et al. 2013). Randomized controlled trials (RCTs) showed LAIAs and oral antipsychotics to have similar effects, whereas mirror-image and some large cohort studies showed LAIAs to be superior to oral antipsychotics in the prevention of relapse (Kane et al. 2013). Large-scale naturalistic studies (see Zhornitsky & Stip 2012) also suggest major benefits of LAIAs, particularly among first episode patients (FEPs).

LAIAs can have many advantages over oral antipsychotics and many patients may prefer LAIAs for

different reasons (see Kim et al. 2012, Yeong & Lee 2013, Kane et al. 2013). High relapse rate caused by partial or complete non-adherence could be successfully prevented by LAIAs. Specifically, patients often forget to take oral medication, which can be potentiated by illness itself because of disorganization, lack of insight and various cognitive dysfunctions. With LAIAs such problems disappear. LAIAs also can contribute to reducing family tension and conflict about medication adherence decreasing the need of family members to check on or remind the patient to take medications. Further, LAIAs application is usually associated with more stable plasma drug concentrations with less fluctuation from hour to hour and day to day. Individual differences in absorption and metabolism of oral antipsychotics can lead to significant and unpredictable variations of plasma drug concentrations with unwanted clinical consequences.

There are also on the other side some limitations related to the LAIAs strategy. The nine, in Croatia six, in other countries even less number available LAIAs are beneficial, but limited because they do not mirror the much larger number of oral antipsychotics at the therapeutic disposition. Quite a number of patients has negative attitude towards depot injections due to the limited or wrong information. Some of them can be feared of being controlled when treated with LAIAs, others may be feared that injections are painful (Yeong & Lee 2013). The fear of needle may be also a reason why some patients refuse LAIAs. For some patients and/or their families injectable treatment means a more severe illness.

The optimal treatment regime, in terms of antipsychotic selection, dosage, duration, effectiveness (efficacy and tolerability) is individual and should be person-centred. Patients bring unique characteristic related to their vulnerability, resilience or recovery potential and potential for psychological and spiritual growth. The proper LAIAs treatment should be offered whenever it may get an advantage to patients with schizophrenia, particularly to FEPs or those who have high risk for it. Despite the proved benefits, prescription of LAIAs is not a guarantee of adherence because the patient can still escape to come for their two, three or four week injection. However, LAIAs provide the advantage of prompt recognition of non-adherence when a patient misses a scheduled injection, while non-adherence to oral antipsychotics is difficult to detect. The individual patient preference is very important. Linking LAAIs to the patients' individual goals and desires may significantly contribute to the achieving therapeutic alliance and better treatment outcome. Motivational interview and informed consent should help patients to experience possible choice of maintenance LAIAs treatment as his/her good choice. Helping patients decide to try LAIAs and stay on them is an important goal of therapeutic contract. If the principles of creating favourable treatment context and fostering patients' creativity (see Jakovljevic 2013b) are followed, the majority patients with schizophrenia will be proactively LAIAs treatment adherent.

Rethinking treatment goals with LAIAs and changing fundamental treatment philosophy: The critical period concept

The LAIAs have long been considered as a treatment reserved only for non-adherent patients with frequent relapses or who pose risk for others. Recently, with regards to the schizophrenia staging and critical period concept, the interest of using SG-LAIAs in the early stage of schizophrenia has increased. Schizophrenia is a group of the long-term neurodevelopmental and neurotoxic disorders manifesting itself through several stadiums: pre-symptomatic high-risk or stage1, prodromal or stage 2, psychotic or stage 3, and chronic illness or stage 4 (see Insel 2010). With the time passing schizophrenic disorders manifest with repeated psychotic episodes with varying levels of inter-episodes remission as well as with increasing disability and mental deterioration following each episode. The relapse rate after first episode schizophrenia is 16% during the first year and rises to more than 50% at two years and more than 70% at five years (see Kaplan et al. 2013). Patients often show decreased treatment response following a relapse and increased time to remission may follow each subsequent relapse (see Potkin et al. 2013). Experience during every psychotic episode is imprinted in the neuroplasticity map so that every new episode makes predisposition for the next one (sensitisation and kindling mechanisms).The bulk of mental deterioration seems to occur in the critical period of the first five years of illness (see Yeong & Lee 2013) after which negative symptoms become predominant. Relapses seem to be associated with loss of brain tissue and diminished probability of achieving a full recovery and each relapse worsens the prognosis of illness and increase direct and indirect health costs (Viala et al. 2012, Getzen et al. 2013). Probability for recovery is the highest at the first episode and with continued long-term treatment (see Potkin et al. 2013). After first episode many patients are non-adherent to oral antipsychotics because they have not fully accepted the reality of their diagnosis and because they have often a false sense of not needing continued drug treatment. Therefore, the relapse prevention and achieving full personal recovery, particularly in the critical period of illness, is crucial for the successful management of schizophrenia. Rethinking schizophrenia as a neurodevelopmental disorder with psychosis and neurodegeneration as a late, potentially preventable stage of illness (Insel 2010) yields new perspective on SG-LAIAs utilization in early stages of illness.

The general attitude in psychiatry toward LAIAs is still prevailing negative because depot antipsychotics are considered old-fashioned, risky due to side effects, stigmatizing and less acceptable to patients, particularly

in FEPs (Kim et al. 2012, Llorca et al. 2013). According to data from literature, LAIAs are underutilized in many countries despite their potential advantages that minimise the risk of relapse, improve global outcomes and contribute to better recovery (Parellada et al. 2012, Rossi et al. 2012, Lambert 2013). Many psychiatrists led by official treatment guidelines favour oral antipsychotics and consider LAIAs only after successive relapses due to treatment non-adherence. Barriers to more rational and creative utilizing LAAIs are many not involving only psychiatrists', but also GPs and patients' attitudes and preference for oral treatment. It is very important to overcome LAIAs indication bias in order to be able to utilize all available therapeutic potential in the long-term management of schizophrenia. Changing treatment philosophy may be a critical step towards overcoming what some view as „therapeutic stagnation in psychiatry" and providing better treatment effectiveness and efficiency for patients benefit. A "paradigm shift" is needed from the mechanistic, formistic and reducionistic way of thinking to contextual and systemic thinking with new treatment holodigm regarding LAIAs in schizophrenia treatment. There is much room for improvement in pharmacotherapy of schizophrenia by individualizing and personalizing LAAIs treatment in a more creative manner. Creative instead a more dogmatic approach to treatment guidelines (Jakovljevic 2013a, b, c) could advance everyday clinical practice with SG-LAAIs as a fundamental treatment option for the long-term management of schizophrenia. Having in mind the nature of schizophrenia, the frequency and consequences of relapses with psychotic episodes and high rates of non-adherence in oral antipsychotics taking, it is quite reasonable to consider LAAIs as a fundamental strategy to be offered to patients, particularly in early stages of disease and FEP patients.

Lessons to be learned from post-injection syndrome monitoring: In every adversity there is a seed of opportunity

Patients who receive LAI olanzapine must be monitored for at least three hours after each dose in a appropriate health-care facility due to the possible development of post-injection delirium/sedation syndrome which occurs in 0.07% of injections and in approximately 1.4% of patients (see Atkins et al. 2014). At first glimpse this 3-hours observation period may seem as a disadvantage. However, the observation time may be used for psycho-education and creative workshops for patients promoting their well-being and personal recovery. The treatment context constitutes the ritual and different symbolic elements of the therapeutic act with LAIAs which may be related to placebo or nocebo response. Patients are not just neurobiological objects who respond only neurochemically to LAIAs, but also subjects who respond to meaning that LAIAs have for them (see Jakovljevic 2013b). The creation of favourable therapeutic context may significantly increase or maximize placebo and decrease or minimize nocebo response to LAIAs (see Jakovljevic 2014). The purpose of LAIAs is to empower the patients to control their disease, to obtain full personal recovery and to regain control over their life. However, LAIAs application and pharmacotherapy in general are often not enough for full treatment success. LAIAs as a sole form of treatment may carry a terribly unhelpful message that patients don't have to change their life style and don't have to learn any new skills, they just have to receive their medication on time because the only problem is in brain chemistry. LAIAs are one essential external support, alongside a whole range of other type of resilience-promoting supports, skills and strengths. The goals of LAI antipsychotic treatment are not only to prevent relapse, but also to improve neuroplasticity and help patients learn new ways of thinking, emotional response and behaviour to get more love, freedom, power, joy and sense of life. Personal recovery involves a journey from disengagement to engagement, from surviving to living and growing, it has many routes and each patient's journey is unique with taking back control over own life and finding hope for a better future (see Slade 2009). Love (attachment, connecting, belonging), freedom (choice, independence, autonomy), power (learning, achievement, control), joy (fun, play, pleasure, enjoyment), and purpose (meaning, sense of life) are important components of personal recovery. Loss of a sense of self which is replaced by a role or identity as a mental patient, loss of power and freedom, including agency, choice and personal values, loss of meaning, such as through loss of valued social roles and loss of hope, leading to give up and withdrawal (Spaniol et al. 1997 according to Slade 2009). Developing a positive identity, framing the 'mental illness', self-managing the mental illness, developing valued social roles, puting into practice more love and meaning are important tasks of personal recovery oriented treatment with LAI antipsychotics.

Conclusions

Despite a growing consensus based on number naturalistic studies for the superiority of LAAIs over oral equivalents due to improved adherence and more stable pharmacokinetics, many current official treatment guidelines recommend basic treatment with oral antipsychotics. In recent years the interest of using SG-LAAIs, particularly in the early stages of schizophrenia, has increased in order to improve treatment outcome and prognosis of illness. Schizophrenia should be treated with antipsychotics earlier and for longer periods of time, and thus LAIAs may be optimal choice what is also suggested in some recent treatment guidelines. Any patient for whom long-term antipsychotic treatment is indicated should be offered LAAIs. Given the well-recognised relationship between non-adherence and risk of relapse, patients who are irregular in taking medications are must-offer candidates for LAAIs.

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