ETHICAL APPROACH TO PREVENTION OF SCHIZOPHRENIA - CONCEPTS AND CHALLENGES
Kresimir Radic1, Marko Curkovic1, Dario Bagaric2, Maja Vilibic3, Andrea Tomic1 & Maja Zivkovic1

1University Psychiatric Hospital Vrapče, Zagreb, Croatia
2Graduate Entry Medical School, University of Limerick, Ireland
3University Hospital Center "Sisters of Mercy", Zagreb, Croatia

received: 16.1.2017; revised: 12.10.2017; accepted: 29.12.2017

SUMMARY
Patients with schizophrenia, nowadays chronic, frequently disabling mental disorder, get initial treatment after detection of a psychotic episode, seemingly late, potentially preventable stage of illness. As our knowledge about the nature of schizophrenia and other diseases of the spectrum is growing, so are the early interventions becoming more possible, and it is important to conceptualize the clinical, legal and moral issues emerging with new preventive treatments. Every intervention, especially in pre-clinical population, demands a careful risk-benefit assessment and having basic bioethical principles - primacy of patient's welfare, beneficience/non-maleficience, autonomy and justice - in mind. We believe that pharmacological treatments, considering today's drugs safety and effectiveness profiles, should stay reserved for cases with highly probable negative outcomes to patient's wellbeing, and that all other low-risk interventions, like psychosocial treatments, should be considered for reducing the conversion to disorder, if possible, or relieving the distress in vulnerable persons, when such vulnerability gets detected. How to recognize persons at risk before the start of the disorder, without missing the majority of cases or burdening healthy persons with stigma, is another challenge and not only mental health professionals should be included in finding the solutions. The broadest public, and especially the experts that will build the safety-net for the at-risk individuals, should get best possible appropriate education about the schizophrenia in order to stigmatize less and help more.

Key words: ethics – medical - early diagnosis - family health - genetic predisposition to disease - risk factors - primary prevention – schizophrenia - prevention & control

INTRODUCTION
After considering a great number of neurobiological, clinical, genetic and epidemiological research findings, biological psychiatrists can now agree schizophrenia is a neurodevelopmental disorder, with genetic and (prenatal and later) environmental factors playing a significant role in its etiopathogenesis. Its highly variable course and clinical phenomenology, an outward of aberrant CNS structures, is a result of nonlinear interactions of genetic factors among themselves and with multiple and various environmental factors, all with variable timing, duration, and severity (Maric & Svrakic 2012). Patients with this nowadays chronic, frequently disabling mental disorder get initial treatment after detection of a psychotic episode, seemingly late, potentially preventable stage of the illness (Insel 2010, Jakovljevic 2011, Haller et al. 2014).

A number of studies highlighted cognitive decline as a detectable core feature of schizophrenia, with psychosis happening in the later stages of development (Kahn & Keefe 2013, Keshavan et al. 2010), so the new high aim was set: initiating treatment as early as possible, even prior to the emergence of positive symptoms, including hallucinations and delusions, in order to have patients’ long-term functioning remediated and maintained (Comblatt et al. 2012). In addition to treatment, prevention might become a crucial way to reduce the public health and high-emotional burden of schizophrenia. It seems primary prevention could be a feasible strategy in tackling depression (Cuijpers et al. 2008), but some additional issues arise when considering actions for preventing the onset of schizophrenia, one of the leading causes of long term disability worldwide (Muesser & McGurk 2004, Vos et al. 2015). In essence, addressing the schizophrenia risk properly and developing evidence-based targets for primary prevention of schizophrenia are crucial and somewhat specific issues that need to be considered, together with the ethical questions they raise.

GENETIC SCREENING: AN EARLY OMEN OR A PROMISE?
In 1962, American Psychological Association's president Paul Meehl coined the term 'schizotaxia', a genetic predisposition to schizophrenia, or rather “an integrative deficit predisposing to schizophrenia, and of genetic origin” (Meehl 1989). Originally a heretical model, following findings that about 8-15 percent of children with parent with schizophrenia would develop the disorder themselves (Jablensky 2010, Erlenmeyer-Kimling et al. 1995, Niemi et al. 2004, Parnas et al. 1993) - a rate that is about ten times greater than estimated occurrence of schizophrenia in general population - schizotaxia idea is largely explored, today
conceptualised with multifactorial polygenic etiology (Tsuang et al. 2002) in interaction with environmental influences throughout a person’s lifetime (Nelson et al. 2013), manifesting itself with neuro-psychological, social and symptomatic impairments from the early age (Cornblatt et al. 2012, Seidan & Nordentoft 2015). Since a various degree of compensation, in relation to the levels of expression of a proposed disease process, is to be expected in vulnerable person, shizotaxia is seen as a quasi-dimensional concept (Nelson et al. 2013), and studies have shown that psychotic symptoms in first-degree schizophrenia relatives are associated not only with schizophrenia, but with other disorders of a schizophrenia spectrum risk as well (Onstad et al. 1991) and that non-psychotic relatives of schizophrenia patients have observable schizotypal, “schizophrenia-like” traits at higher rates than in healthy comparison subjects (Kendler & Gardner 1997).

Once the phenomenology before the diagnosis of the disorder became the focus of the researchers, somewhat confusing or overlapping terminology for the risk groups emerged, so the exhaustive explanations for underlying concepts and criteria should be looked up (Schultze-Lutter et al. 2011). In short, genetically vulnerable persons initially show unspecific complaints and symptoms, then somewhat predictive basic symptoms: subtle, subclinical self-experienced disturbances in thought, speech, and perception processes that are rarely perceivable from outside. Next, some detectable (attenuated, limited) psychotic symptoms can be spotted in fraction of the cases, before the first psychotic episode (Schultze-Lutter 2010). Ultra-high or high clinical risk criteria vary between research groups and mark the imminent conversion to psychosis. That said, models for detecting persons at high clinical risk have emerged, and they feature the genetic component of the risk, various symptoms, social impairment and drug use as baseline predictors (Cannon et al. 2008).

Considering that even when the prediction is applied in the persons with inconclusive symptoms seeking treatment, identified as ones at ultra-high risk, the conversion to psychosis happens in some 30-40 percent of cases (Cornblatt et al. 2012, Fusar-Poli et al. 2012), and knowing that a majority of cases of schizophrenia has no clear family history, it is obvious that designating risk is a practical, and therefore an ethical challenge (McGlashan et al. 2001).

So, in order to predict the persons at risk before the start of the disorder, without missing the majority of cases or burdening healthy family members with stigma, one day genetic analysis might be considered as necessary. But genetic screening for any clinical purpose should be tied to the availability of empirically verified intervention, proposes American College of Obstetricians and Gynecologists (2008). American Society of Human Genetics Board of Directors and American College of Medical Genetics Board of Directors state (in 1995): "If the medical or psychosocial benefits of a genetic test will not accrue until adulthood, as in the case of carrier status or adult-onset diseases, genetic testing generally should be deferred. Exceptions to this principle might occur when the adolescent meets conditions of competence, voluntariness, and adequate understanding of information."

A thoughtful assessment of medical necessity is a must before any diagnostic tests, and while some societies might offer schizophrenia screening as a part of routine care for high-risk families, some will not, which is a policy matter. The counselling and strict regulation of screenings can prevent misinformation, misinterpretation (unnecessarily alarming) and stigma.

Which population would get screened for common schizophrenia gene variants (or some novel biomarkers) matters (Ayalew 2012): an imaginative and novel statistical framework could boost the power of such screenings to a point when an application to not only high-risk individuals would become possible, spreading the schizotaxia concept even further. And if prenatal genetic screening for schizophrenia ever appear, the affluent couples without family history of schizophrenia would use it, wanting a healthy offspring, and the risk of careless test result interpretation could become a serious matter. Noninvasive prenatal diagnosis, offering more than only early detection of genetic disorders, already receives a warning for trivialization of abortion (Benn 2010), and pregnancy termination is one of the most contentious ethical and political issues.

The consensus about the level of acceptability of genetic determinism has not yet been built and the discussion transgresses the scopes of our subject, but we imagine that serendipitously discovered, high-risk pregnancies might get terminated, or, because of inadequate state programme funding, high-risk, stigmatized children rearing poorly supported from that point onward.

**INTERVENTIONS: WHEN AND HOW?**

Schizophrenia emerges, usually in young adulthood, after an interplay between genes and the environment, so, a full-blown disease occurs when environmental factors converge. And in certain phases of development the appropriate targets could be considered in reducing the rate of later conversion in persons at risk (Seidman & Nordentoft 2015).

Some early interventions, especially the unspecific but beneficial measures for child development, could be done relatively harmlessly: pregnant mothers can get screening to toxoplasmosis, connected with not only higher risk for psychosis (Torrey & Yolken 2003). Also, famine should be avoided in pregnancy, and lower birth weight, with other birth complications, prevented as well. Traumatic experiences in childhood should be reduced, and special care should be given to immigrants and refugees, since the prevalence of some psychiatric disorders can be higher in their population (Rapoport et al. 2012).

All the mentioned interventions can be done no matter of the detected schizophrenia risk, but we
underline the importance of their implementation to families at risk, as well as giving a greater focus to relieving the burden of the disorder and the reduction in quality of life (Margett et al. 2013) with needed social or psychiatric interventions and helping with enabling good, supportive parental care and reducing demoralization, poverty, social exclusion and other forms of suffering. There are other preventive measures that could be beneficial to the mental health of the persons no matter of the risk of conversion to psychosis, especially drug or alcohol use prevention programmes, since persons with family case of schizophrenia and use disorders have a greater rate of conversion to psychosis (Cannon et al. 2008), and also because history of substance abuse has been connected with violence in psychotic episodes (Volavka et al. 1997).

And some new experimental targets need to be mentioned: for example, supplementation of mother's diet with choline as the means of in-utero intervention is a promising, creative and personalised approach that should be additionally explored (Freedman & Ross 2015, Ross et al. 2013). There is also a proposal for adding omega-3 fatty acids or N-acetylcysteine (an antidote to paracetamol poisoning) to a child’s at risk diet, in order to diminish the developmental anomalies caused by oxidative stress or neuroinflammation, before the onset of the disorder (Amminger et al. 2010, Berk et al. 2013, Do et al. 2015, McNamara et al. 2015, O’Donnell et al. 2014, Steullet et al. 2014) that could be considered as well. Benefits of such interventions, in terms of effective reduction of conversion rate to schizophrenia and, consequently, in terms of efficiency, shall be clear in two decades or more, after long-term studies complete, and the ethical challenge in discharging ongoing relationship with participants, considering that the efficacy would be determined much later after the participation in research, was recognised (Appelbaum 2015).

Most of the targets mentioned before could be applied without harming the persons identified at risk, and very early as well, before any symptoms occur, and therefore, with relatively easier ethical dilemmas. A few studies, tracing impairments in families at risk, from perinatal period onward, with various early interventions as a goal, are ongoing (Seidman & Nordetoft 2015), and some others trials have already shown some benefits of giving low-dose risperidone to adult, first-degree relatives with impairments in several measures of clinical, neurocognitive and social function: up to 2 milligrams of risperidone a day could attenuate some schizophrenia-related cognitive and social difficulties in adults with schizotaxia (Stone et al. 2015). And in another, seven year long study, a marked improvement in cognitive, social, and vocational functioning of seven relatives of patients with schizophrenia has been brought about by continuous use of 1-2 mg risperidone a day (Rybakowski et al. 2007). But translating those findings to recommendations for low-dose antipsychotic use from the childhood, when first cognitive problems in families with schizophrenia occur (Seidman et al. 2013.) would be premature, since relatively few published data on adverse events of risperidone or other antipsychotics in that class in adolescent patients are available (Pringsheim et al. 2011). And before the grasp on the subject gets possible, another ethical issue should be tackled: psychiatric research in minors, with intervention containing more than minimal risk of harm. Such ethical challenge is addressed in one study of prodromes as beneficial for participants to justify the risk, with benefit at least as favourable as the alternative (watch and wait), and by providing two informed consents, one from parent and one from an adolescent (McGlashan et al. 2001). However, would such criteria stand in targeting cognitive impairments in 7-year-olds pharmacologically? Considering the now necessary rate of false-positives - ever greater in every step prior to apparent psychosis - we could say the risk is not appropriate for the level of benefit in the anecdotal studies with currently available antipsychotic drugs.

Recent reports on cognitive remediation therapy in patients with schizophrenia find that younger patients with less cognitive deficit benefit the most (Keshavan et al. 2014, Kontis et al. 2013), so maybe this option could be given to minors at risk when first sign of deficit is detected. If the intervention in such early phase shows great efficacy, exposing high-risk family members to brain neuroimaging in childhood could provide a valuable insight in neurodevelopment (Rapoport 2012) and the opportunity to prevent the progression.

**PRODRONES: ‘LAST MINUTE’ IS IMPORTANT**

A prodromal period of one to three years precedes schizophrenia, when a behavioural change and functional deterioration, as well as various psychotic symptoms might occur. Up to 40% of persons with prodromes referred to clinical services gets schizophrenia within 12 months, so a delay or prevention of conversion to psychosis is rather important (Combatt et al. 2012; Haroun et al. 2006, Stafford et al. 2013). Some researchers find that people with prodromes are already ill and do not only need preventive intervention but also treatment (Ruhrmann et al. 2010.), although the diagnosis cannot be given yet; but others, in contrast, propose that favourable environment might even result with some benefits in, for example, creative life areas of a high-risk person (Ayalew 2012) and wonder whether such benefits could be lost if they get medicated or stressed about the risks. Considering the findings that more than 50 percent of detected persons will not convert to psychosis, some propose that monitoring of mental state, supportive therapy, and attention to current practical needs would be sufficient. Since it can be self-limiting in the majority of cases, regular assessment of mental state to detect first episode of psychosis is indicated, in order to provide treatment - from mild psychological support and family stress reduction (Yung...
et al. 2012) to pharmacotherapy and hospital stay, if necessary - so that the worse-case scenarios, violence and suicide, get prevented (Large & Nielsen 2011, Vilibić et al. 2015).

WHO CARES?

The complexity of practical and ethical challenges surrounding current state of research on possible primary prevention of schizophrenia, with unsubstantial data on many critical points, cannot be solved without a collaborative work of many experts. Some common pathways are obvious, starting in the psychiatric office after an adult with schizophrenia is provided with initial care and adult family members with the information about the risks for them and their offspring, but getting the support from that point onward could get complicated. Much of the work in stigma reducing should be done immediately afterwards by pediatricians, school or family physicians, social care providers and various therapists, which means not only health care system, but social services and schools would be involved, if necessary. The capacities for such approach should yet be built.

Whoever gets involved, the possibility of schizophrenia development in at-risk child's later life should be explained properly and competently. It could introduce additional stress and tension in entire family, so the information, reassurance or even referrals should be given as gently as possible, in order to reduce discrimination. Offered help should introduce as less harm as possible, especially in the earliest phases.

CONCLUSION

Lucy van Pelt told Charlie Brown: "In all of mankind's history, there has never been more damage done than by people who thought they were doing the right thing." (Shultz 1971)

Our knowledge about the nature and the spectrum of schizophrenia development is growing, and the possibilities of the interventions are greater than ever. That raises the need to address possible clinical, legal and moral issues in this field. Targeting the vulnerable persons without clearly indicated clinical treatment needs the assessment of risks and benefits. It will be a great challenge to construct a valid screening procedure for appropriate risk detection without harming a number of false-positive young people with stigma and adverse effects of medication, or wasting a great amount of public resources on a large-scale therapeutic interventions with limited effectiveness. However, when such screening procedure becomes available to persons with relatives suffering schizophrenia, we propose revisiting appropriate proven targets to prevent or delay the onset of a full-blown disorder, but with great focus on patient welfare, autonomy, justice and stigma reduction. The broadest public, and especially the experts that will build the safety-net for the at-risk individuals, should get best possible appropriate education about the schizophrenia in order to stigmatize less and help more: it is a bare minimum that families that suffer deserve.

Psychopharmacological interventions should be reserved for cases with very high certainty that patients’ well-being is at stake, no matter in which point of the dimension does a person at risk reside. Low-risk interventions are more appropriate as the early targets in the broadest risk groups, but their efficacy should be explored. We underline the importance of the addiction prevention in persons at risk for schizophrenia, in order to avoid the progression to psychosis and possible violent outbursts.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Study conception and design: Kresimir Radic, Marko Curkovic & Maja Zivkovic;

Aquisition of data, or analysis and interpretation of data: Kresimir Radic, Marko Curkovic, Dario Bagaric, Maja Vilibic, Andrea Tomic & Maja Zivkovic;

Drafting the article or revising it critically for important intellectual content: Kresimir Radic, Marko Curkovic, Dario Bagaric, Maja Vilibic, Andrea Tomic & Maja Zivkovic;

Final approval of the version to be published: Kresimir Radic, Marko Curkovic, Dario Bagaric, Maja Vilibic, Andrea Tomic & Maja Zivkovic.

References


REFERENCE IN PROOF] doi: 10.1016/j.schres.2014.06.021

Correspondence:
Krešimir Radić, MD
University Psychiatric Hospital Vrapče
Bolnička cesta 32, 10 000 Zagreb, Croatia
E-mail: kresimir.radic@bolnica-vrapce.hr