Towards personalized pharmacotherapy for suicide prevention across the lifespan

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Using genomics to predict antidepressant response in suicidal depressed children

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Background Depression and anxiety disorders are among the most common childhood psychiatric disorders. Selective serotonin reuptake inhibitors (SSRIs) are generally considered first-line treatment for both depression and anxiety in this age group. However, it has been reported that 30%–40% of all patients who receive a sufficient dose and duration of treatment fail to respond. Moreover, SSRI use is frequently associated with serious adverse events (SAE), including activation symptoms, manic switch and increased suicidal behavior. These are particularly relevant in pediatric populations because of concerns about the suicide threat of SSRIs, resulting in a black-box warning. Currently there is no way of knowing in advance who of the patients will respond. Identification of biomarkers that would be early predictors of response and of the occurrence of SAE could help to maximize the benefit–risk ratio for the use of SSRIs, and speed up the matching of treatment to patient. The main objective of this project is therefore to identify and validate biomarkers predicting response and SAE in depressed children and adolescents, thus improving treatment, enabling the development of novel diagnostic tests and suggest novel therapeutic targets for future related drug development.
Methods As a preliminary pilot, we already obtained blood samples from 80 depressed and anxious children and adolescents over the last year before, during and after eight weeks of fluoxetine (FLU) therapy. Genetic and epigenetic samples were collected from all participants. The patients were treated with FLU 20–40 mg/day for 8 weeks. Clinical response was measured with several scales including the Children's Depression Rating Scale–Revised (CDRS-R), the Beck Depression Inventory (BDI) and the Screen for Child Anxiety Related Emotional Disorders (SCARED).
Results The participant's age ranged from 6 to 18 (14.12 ± 2.30) years. The overall response rate was 56%. Ten percent responded with SAE. Regarding Pharmacogenetics, The 5-HTTLPR ss genotype was associated with a poorer clinical response with regard to depressive symptoms as well with fewer reports of agitation compared to the ll genotype. Regarding immune measures, we analyzed cytokine levels from 41 children. Plasma concentrations of TNF-α, IL-6 and IL-1β were measured by enzyme linked immunosorbent assays (ELISA) before and after FLU treatment. Antidepressant treatment significantly reduced TNF-α levels ($P = 0.037$), with no significant changes in the levels of IL-6 and IL-1β. All three pro-inflammatory cytokines were significantly ($P < 0.05$) higher in SSRI-refractory than SSRI-responsive patients, i.e.: higher levels of TNF-α, IL-6 and IL-1β might predict non-response to fluoxetine treatment in children.
Future plans Out of the study sample we selected 13 remitters and 13 non-responders and 10 children with SAE (activation symptoms, manic/hypomanic switch, increased suicidality), and analyzed expression profiles in peripheral blood at admission and after 8 weeks of treatment using illumine Truseq technique. Hopefully, we shall find significant differences in miRNA profiles between the different groups which may serve as biomarkers indicating AD treatment response and SAE. The differentially regulated miRNA's can be studied in depth in the future in animal models in order to support the hypothesis that they may be involved in the AD mechanism.
Disclosure of interest The authors have not supplied their declaration of competing interest.

http://dx.doi.org/10.1016/j.eurpsy.2016.01.926

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Large-scale suicide prevention by pharmacological treatment of mood disorders

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Introduction In psychological autopsy studies, at least half of suicides have suffered from depressive or bipolar disorders at time of death. Improving access to care and provision of evidence-based pharmacotherapies can be important preventive measures.
Objectives To examine suicide risk and pharmacoepidemiology in mood disorders; evidence for efficacy of pharmacotherapies in mood disorders and in preventing suicidal behaviour in them, and limitations to effectiveness of treatment due to problems of adherence.
Aims To evaluate potentials for suicide prevention in mood disorders by improved access to treatment, improved quality of treatment provision, improved adherence, or by specific pharmacotherapies.
Methods Selective review of literature.
Results Risk of suicide death and attempts in mood disorders clusters into major depressive and mixed illness episodes, and time spent in them is a major determinant of risk, but direct evidence for preventive effects of effective pharmacotherapies remains limited. Observational and randomized studies indicate lithium treatment to reduce risk of suicide deaths and attempts. Ecological evidence from Europe shows increasing sales of antidepressants to consistently associate with declining regional suicide rates. Forensic chemical studies still find majority suicides negative for antidepressants. Poor adherence is a central problem in treatment provision.
Conclusions Positive impact of increase in pharmacotherapy provision in the last few decades on suicide mortality remains uncertain. Lithium is the pharmacological agent with best evidence for preventive utility, but underused. Providing treatments for those at risk, improving quality and continuity of treatment, and integrating them with psychosocial approaches is likely to be beneficial for suicide prevention.
Disclosure of interest The author has not supplied his declaration of competing interest.

http://dx.doi.org/10.1016/j.eurpsy.2016.01.927

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Brain imaging biomarkers in personalizing pharmacotherapy of suicidal depressed patients

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Background New knowledge has emerged about decision-making, mood regulation, social distortions and learning that is relevant for the diathesis for suicidal behavior. All four domains have identified underlying neural circuits and for decision-making and mood regulation also specific neurotransmitter systems.
Methods We have conducted PET studies of the serotonergic system and CSF studies of the serotonin, norepinephrine and dopamine neurotransmitter systems in patients surviving suicide attempts to determine whether they have neurotransmitter abnormalities that resemble those found in the brain after suicide. We found