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.
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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.
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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

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alterations in the serotonin transporter and the 5-HT_{1A} receptor that are similar to those seen in suicides and moreover the severity of the abnormality in 5-HT_{1A} binding is correlated with the lethality of suicidal behavior. Other studies examining CSF levels of 5-HIAA are consistent with imaging data and extend the findings to the noradrenergic and dopaminergic systems. Finally, we will present data on use of these biomarkers to predict treatment outcome. Abnormal decision-making and mood regulation in suicidal patients is linked to abnormal brain biology and has direct implications for clinical practice in terms of selecting specific types of medication and how these may be best combined with psychotherapies.
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Age and pharmacotherapy of suicidal depressed bipolar patients

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The mortality and morbidity due to suicidal behavior associated with bipolar disorder is the greatest among psychiatric diagnoses. To address this problem, it is essential to find predictors of future risk as well as protective factors. Studies from several international teams have demonstrated that for bipolar disorder, the presence of a depressive episode is the most robust predictor and risk increases as does depression severity. Protective factors such as older age and religious affiliation are also key moderators. The role of pharmacotherapy in suicidal behavior has been studied mostly utilizing data that are either observational and naturalistic, rather than experimental. Only one randomized, double-blind clinical trial has been conducted to date, although another one is underway. The comparison of lithium and valproate in terms of effect on suicidal behavior revealed no differences. Although the trial was not powered to detect small effect sizes, results suggest that the Relative Risk ratio generated from meta-analytic studies (RR$\sim$ 5) is too optimistic. The trial also suggested that younger individuals may respond differently to pharmacotherapy, suggesting opportunities to personalize treatment approaches. Robust pharmacotherapy targeting both mood stabilization and depressive symptoms is essential and may assist in the quest against suicidal behavior.
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Treatment of people with dual diagnosis

S114

Treating adult ADHD and comorbid substance-related disorders

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Attention-deficit/hyperactivity disorder (ADHD) is a complex, and multifactorial and chronic neurodevelopmental disorder. Comorbid psychiatric disorders are highly prevalent in individuals with a diagnosis of ADHD. There is a solid overlap between ADHD and substance use disorders (SUD). Prevalence of SUD is high among patients with ADHD, so that SUD are approximately double as common among individuals with ADHD than in general population, and individuals with SUD have much higher rates than expected of a comorbid ADHD. Studies shown that treatment during childhood of attention-deficit/hyperactivity disorder with stimulant medication neither protects nor increases the risk of later substance use disorders. Nevertheless, recent studies found that patients with ADHD and SUD can reduce ADHD symptoms and SUD with stimulants and cognitive-behavioral therapy. Treatment of ADHD in patients with SUD requires a comprehensive diagnostic assessment. It is recommendable to stabilize the addiction prior to treating the ADHD. In this talk, the recent literature for the treatment of adults with co-occurring ADHD and SUD will be reviewed.
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Value-based health care

S115

Value in mental healthcare: The patient aspect

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From the patients' point of view, valued-based mental healthcare is mental healthcare based on a holistic vision of care, according to which patients are actively involved in their treatment to achieve the best possible outcomes. They are invited to collaborate with both mental health care providers such as psychiatrists and primary caregivers to determine what types of treatment are the most effective.
GAMIAN-Europe believes that the best package of care includes the following four elements:
– medication – antipsychotic medication is consensually regarded as first-line treatment for people with mental health problems;
– psychotherapy/counselling – although antipsychotic medications are the mainstay of treatment for mental health problems, pharmacotherapy alone produces only limited improvement in negative symptoms, cognitive function, social functioning and quality of life. Additionally, many patients continue to suffer from persistent positive symptoms and relapses, particularly when they fail to adhere to prescribed medications. These situations emphasize the need for multimodal care, which includes psychosocial therapies as adjuncts to antipsychotic medications in order to alleviate symptoms and to improve social functioning and quality of life;
– psycho-education – the more a patient learns about his/her condition the better placed he/she will be to take control of it. Psycho-education embodies this principle by using a clearly-defined therapeutic programme, in which a trained therapist delivers targeted information designed to reduce both the frequency and the severity of symptoms. Psycho-education increases patients' knowledge and understanding of their illness and treatment options and helps them cope more effectively. Many people find that they benefit not only from the information they receive during psycho-education, but also from the learning process itself. There are several different ways in which psycho-education can be delivered, including one-to-one sessions with a therapist, sessions aimed specifically at carers and family members, group sessions attended by several people coping with mental illness and mixed group sessions attended by people with mental illnesses and family members;