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Joint Symposia

Joint symposium: How long do we have to wait for the antidepressant effect?

JS001

Joint symposium: How long do we have to wait for the antidepressant effect? Mechanisms of action for delay of onset response to antidepressants

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Major depressive disorder (MDD) is a severe psychiatric syndrome with very high prevalence and socioeconomic impact. Monoamine-based antidepressant drugs (AD) display slow onset of action and limited efficacy. Preclinical studies show that ADs trigger a series of slow adaptive mechanisms that limit the clinical response. These mechanisms result from the pharmacological blockade of monoamine transporters (SERT, NET) and involve presynaptic, such as autoreceptor desensitization (e.g., 5-HT_{1A} and 5-HT_{1B} for serotonin neurons) as well as postsynaptic mechanisms, such as increased neurogenesis and expression of trophic factors, increased dendritic complexity, etc.

Given the strong homeostasis of serotonin and noradrenaline neurons, a way to improve antidepressant action is to prevent self-inhibitory presynaptic mechanisms mediated by auto- and heteroreceptors after reuptake blockade. This strategy was used in the past with the non-selective 5-HT_{1A} antagonist pindolol and has been incorporated by two recently developed AD (vilazodone and vortioxetine). Likewise, new molecular strategies using RNA interference (RNAi) show that the modulation of gene expression in serotonin neurons offers a great potential. Hence, local or intrnasal administration of small interfering RNA (siRNA) molecules targeting SERT or 5-HT_{1A} autoreceptors evokes rapid and robust antidepressant-like effects in rodents.

Moreover, glutamatergic drugs such as the non-competitive NMDA receptor antagonist ketmaine, offer a potential for the development of fast-acting AD due to its rapid and persistent antidepressant effects in treatment-resistant unipolar and bipolar patients after single i.v. infusion, an effect that likely involves the activation of AMPA receptors in ventral areas of the cingulate gyrus and the subsequent fast activation of serotonergic function.

Disclosure of interest F.A. has received consulting honoraria on antidepressant drugs from Lundbeck and he has been PI of grants from Lundbeck. He is also co-author of the patent WO/2011/131693 for the siRNA and ASO (antisense oligonucleotides) molecules.

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JS002

What do clinical trials tell us about antidepressant delayed onset of action?

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Response to antidepressants in major depressive disorder is highly variable and determinants are not well understood. Presentation will provide clinical trial data on time to response and determinants of response to antidepressant treatment. Data is from the Innovative Medicines Initiative funded NEWMEDS collaboration, a large public-private collaboration which assembled the largest dataset of individual patient level information from randomized placebo-controlled trials of antidepressant drugs. Studies were conducted by four large pharmaceutical companies. Dataset includes placebo-controlled trials of citalopram, duloxetine, escitalopram, quetiapine and sertraline in adults with MDD. We examined patient and trial-design-related determinants of outcome as measured by change on Hamilton Depression Scale or Montgomery–Asberg Depression Rating Scale in 34 placebo-controlled trials (drug, $n = 8260$; placebo, $n = 3957$). While it is conventional for trials to be 6–8 weeks long, data presented will show that drug-placebo differences were observable at week 4 with nearly the same sensitivity and lower dropout rates. Having any of these attributes was significantly associated with greater drug vs. placebo differences on symptom improvement: female, patients being middle aged, increasing proportion of patients on placebo, excluding all patients from centers with high placebo response regardless of active treatment response, using active run in periods and including self-report measures. Proof of concept trials can be shorter and efficiency improved by selecting enriched populations based on clinical and demographic variables, ensuring adequate balance of placebo patients, and carefully selecting and monitoring centers. In addition to improving drug discovery, patient exposure to placebo and experimental treatments can be reduced.

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