PROGRESS IN MIND
Resource Center

ECNP Lisbon 2021

CONTENT

4 Why do antidepressants cause emotional blunting and what can be done to resolve it in clinical practice?

6 Major depression can be a family affair, but helping the mother helps the child

8 Emotional blunting: unresolved MDD symptom or effect of treatment?

10 Long-acting injectables together with medical team training may facilitate functional recovery

12 Partial dopamine agonists: wide spectrum of activity and indication

ECNP Lisbon 2021

Welcome to
Progress in Mind Resource Center

This magazine gives you a flavor of the content you will find in www.progress.im, a website brought to you by a dedicated team of medical and healthcare writers whose goal is to deliver the latest news, views and insights relating to a variety of topics within psychiatry and neurology. On this single platform, you can find a mix of face-to-face interviews, current views, webinars, insights from global and local opinion leaders. You can also enjoy timely reporting from international and national congresses to cover your educational needs. The Progress in Mind Resource Center brings you the newest trends and the latest discussions in your field.

Progress in Mind Resource Center also features the Lundbeck Institute Campus – offering in-depth content and resources including image banks and slidekits for your learning and teaching needs.

H. Lundbeck A/S, Ottiliavej 9, 2500 Valby, Denmark

Articles and interviews in this publication have been written by journalists or medical experts on request by Lundbeck. The aim is primarily to focus on psychiatric disease and disease awareness in the congress reporting.

Our correspondent's highlights from the symposium are meant as a fair representation of the scientific content presented. The views and opinions expressed on this page do not necessarily reflect those of Lundbeck.

Constantly refreshed and updated, we aim to make Progress in Mind Resource Center the go-to medical education resource for the busy healthcare professional.

https://progress.im/en

Depression

Why do antidepressants cause emotional blunting and what can be done to resolve it in clinical practice?

Emotional blunting describes an indifferent, unresponsive affect and inability to feel emotions experienced by people with major depressive disorder (MDD) treated with antidepressants.[1,2] Dampening of dopaminergic and noradrenergic input to the prefrontal cortex is thought to play an important role,[3] and management can be guided by understanding the neuropathophysiology.[3]

A negative impact on patient outcome

Emotional blunting is a residual symptom of MDD, which is a symptom experienced by patients with MDD despite antidepressant therapy. Such patients are at risk of relapse.[4]

Emotional blunting can impact everyday patient function and prevent a full functional recovery.[5] More severe emotional blunting is associated with a poorer quality of remission.[6]

> Higher doses of SSRI are more likely to cause emotional blunting[9,10]

Nearly half of patients on all types of monoaminergic antidepressants report emotional blunting,[6] and it is associated with serotonin reuptake inhibitor (SSRI) therapy as follows:[2,5]

- among 161 patients, 46% reported a narrowed range of affect, 21% reported an inability to cry, and 19% reported apathy[7]
- a cross-sectional study of 117 patients revealed that approximately 30% of patients reported some form of apathy[8]

> Lowering SSRI dose8 or changing antidepressant are therapeutic options

What causes emotional blunting?

The primary effect of SSRIs is reduced processing of negative stimuli rather than increased positive stimuli.[9]

Emotional blunting is related to SSRI dose,[9,10] and possibly serotonergic effects on the frontal lobes and/or serotonergic modulation of midbrain dopaminergic systems projecting to the prefrontal cortex (PFC).[10] By enhancing serotonergic transmission, SSRIs can activate GABA interneurons, thereby dampening the noradrenergic and dopaminergic input.[11]

Dorsolateral PFC:

- is primarily associated with "cognitive" or "executive" functions[12]
- appears to play a role in regulating negative emotion through reappraisal/suppression strategies[13,14]
- lesions are associated with significantly higher MDD scores than for head injuries not involving the PFC[12]
- is hypoactive at rest and increases in activity during symptom remission[15]
- Dorsolateral PFC appears to play a critical role in MDD through a defect in regulation of negative affect

Ventromedial PFC:

- is largely ascribed "emotional" or "affective" functions[12]
- lesions are associated with significantly lower MDD scores than for brain injuries not involving the PFC[12]
- is hyperactive at rest and decreases in activity during symptom remission[13]
- Imaging studies suggest a critical link between the automatic processing of emotional signals in the amygdala and the regulation of this activity in the frontal cortex.[16]

Options to resolve emotional blunting are to:

- Lower the dose and/or discontinue the SSRI[8]
- Change the antidepressant to one with a different profile that might improve the patient's emotional response[17]

1. Loas G, et al. Compr Psychiatry 1994;35:366–72.
2. Price J, et al. J Affect Disord 2012; 140:66–74
3. Nutt D, et al. J Psychopharmacol 2007:21;461–71.
4. Conradi HJ, et al. Psychol Med 2011;41:1165–74.
5. Price J. Br J Psychiatry 2009;195:211–217.
6. Goodwin GM, et al. J Affect Disord 2017;221:31–35.
7. Bolling MY, Kohlenberg, RJ. Psychotherapy Psychosomatics 2004;73;380–5.
8. Fava M, Graves LM, Benazzi F, Scalia MJ et al. Journal of Clinical Psychiatry. 2006:67;1754–9.
9. Goodwin GM. Medicographia. 2012;34(3):295–9.
10. Sansone RA, Sansone LA. Psychiatry (Edgmont) 2010;7:14–18.
11. Blier P. Int J Neuropsychopharmacol. 2014;17:997–1008.
12. Koenigs M, Grafman J. Behav Brain Res 2009;201:239–43.
13. Kelley NJ, et al. Front Behav Neurosci 2019;12:337;2.
14. Morawetz C, et al. Soc Cogn Affect Neur 2017;12:569–85.
15. Ye M, et al. PLoS ONE 2015;10:e0133775.
16. Banks SJ, et al. Soc Cogn Affect Neurosci 2007;2:303–12.
17. Godlewska BR, Harmer CJ. Psychopharmacol. 2020; doi.org/10.1007/s00213-019-05448-0.

Depression

Major depression can be a family affair, but helping the mother helps the child

Risk of major depression passes down the generations, according to 38 year follow-up of US families. Increased risk is evident even in the third generation, but most notably when both parents and grandparents have had the disorder. On a positive note, treating a mother's depression to remission improves the prospects for her offspring.

Early and rigorous treatment of major depressive disorder (MDD) in mothers can improve symptoms of depression in their offspring and so help break the cycle of transmission from generation to generation, Myrna Weissman (Columbia University, New York, USA) told APAAM 2021 in a lecture delivered when accepting the Association's annual Award for Research.

Working with her husband, Gerald Klerman (who died in 1992), Professor Weissman developed Interpersonal Psychotherapy (IPT) as an effective, evidence-based tool for the treatment of depression.[1]

The 2021 Award also acknowledged her major contribution to our understanding of MDD through the study of high-risk families who have now been followed for three generations and over 38 years.

> MDD risk was highest in children when both their parents and their grandparents had been affected[2]

Risk of MDD triples in children of high-risk families

In an earlier follow-up that spanned two generations, the risks for MDD, anxiety and substance use disorders among 151 offspring of parents with depression were three times higher than among the children of low-risk families drawn from the same community in New Haven, Connecticut.[3]

At this stage, higher mortality among the offspring of depressed parents was beginning to emerge, and this has now been confirmed at 38 year follow-up. The mortality rate among the offspring of high-risk families is 8.8 per 100, while that in low-risk offspring is 3.8. Deaths from suicide, overdose and accident made a major contribution to the excess mortality, Professor Weissman noted.

But two encouraging features emerge from these longitudinal data. The first is that the risk of MDD extending from affected grandparents into a third generation is attenuated if the second-generation parents are not themselves depressed.[2] MDD risk was highest in children when both their parents and their grandparents had been affected.[2]

> Remission of a mother's depression decreases psychiatric symptoms her children[4,5]

Maternal depression is a modifiable risk factor

Secondly, it seems possible to break the cycle of transmission from one generation to another by effective treatment of affected parents.

The STAR*D-Child sub-study of the larger trial of sequential antidepressant therapy showed that achieving remission of mothers' depression decreases problem behaviors and psychiatric symptoms in their children over the following year.4 Children whose mothers reached remission within the first 3-6 months of treatment showed the greatest benefit.

A mother's improvement helps the child. And this effect is seen both when remission is achieved by medication and when it is achieved by psychotherapy,[5] said Dr Weissman.

Interpersonal Psychotherapy is now widely used across the globe, including rural Uganda, where a cluster-randomized trial showed a group-based approach was highly beneficial in reducing symptoms and dysfunction.[6] An IPT manual published by the WHO is available many languages.[7]

1. Cuijpers P et al. Interpersonal Psychotherapy for Mental Health Problems: A Comprehensive Meta-Analysis. Am J Psychiatry 2016;173:680-7
2. Weissman MM et al. A 30-Year Study of 3 Generations at High Risk and Low Risk for Depression . JAMA Psychiatry 2016; 73: 970–97
3. Weissman MM et al. Offspring of depressed parents: 20 years later. Am J Psychiatry 2006;163:1001-8
4. Wickramaratne P et al. Children of depressed mothers 1 year after remission of maternal depression: findings from the STAR*D-Child study. Am J Psychiatry 2011 ;168:593-602
5. Swartz HA et al. Brief Psychotherapy for Maternal Depression: Impact on Mothers and Children. J Am Acad Child Adolesc Psychiatry 2016 ;55:495-503
6. Bolton P et al. Group interpersonal psychotherapy for depression in rural Uganda: a randomized controlled trial. JAMA 2003; 289: 3117-24
7. World Health Organisation. Group Interpersonal Therapy for Depression 2016; WHO/MSD/MER/16.4

Emotional blunting: unresolved MDD symptom or effect of treatment?

Some evidence suggests that emotional blunting is a side effect of therapy, but other evidence indicates it is an unresolved feature of major depressive disorder, and hence a target for more effective treatment. Where do you stand on this important issue? The question was posed at ECNP 2019 during an Expert Science Exchange.

Treatment of major depressive disorder (MDD) should aim for full functional recovery, and this requires improvement across all domains – cognitive, physical and emotional.1 That is now widely agreed, as is the need for well-tolerated medication essential to promote adherence and so minimize risk of incomplete response and relapse.

Unfortunately, emotional blunting – including feelings of detachment, loss of interest and pleasure – is a common experience during drug treatment, being self-reported by between a third and a half of patients with MDD taking a wide range of antidepressant agents.[2] It is also a frequent reason for patients stopping treatment. In a recent Canadian study of 316 people with MDD, 35% of those who discontinued their medication cited blunted emotion as a cause.[3]

> In a recent study, 35% of people discontinuing medication cited blunted emotion

Emotional blunting may have adverse effects on decision-making and relationships, and result in poor self-care and even thoughts of self harm in an effort to feel emotion.4 Emotional blunting can also be reflected in reduced sex drive and apathy. Any of these features may reduce quality of life.[5] Their presence begs the question: is emotional blunting a consequence of the disease or of its treatment?

Emotional blunting as side-effect

Among others, Guy Goodwin and colleagues from Oxford have drawn attention to the phenomenon of emotional numbing and reduced sensitivity that may appear in certain people treated for MDD. The fact that this can emerge even as depression itself remits suggests the phenomenon is not part of the clinical syndrome but a consequence of its treatment with antidepressant medication.[5]

The case for emotional blunting being an effect of drug treatment was argued by Andrea Fagiolini (University of Siena Medical Center, Siena, Italy). This argument is strengthened, he maintained, by experimental evidence of reduced detection of negative facial emotion found in clinical and neuroimaging studies of healthy volunteers taking antidepressants for as little as a week.[6,7] Importantly, this effect of medication on the perception of emotion is the reverse of that seen in clinical depression, which is associated with increased recognition of negative vs positive facial expressions.

Since patients with clinical depression have an increased ability to recognize negative vs positive facial expressions (negative attentional bias) these data suggest that drug treatment reduces the ability to detect some negative stimuli.

> Medication-induced biases in emotion processing are the opposite of those seen in untreated MDD

Moreover, there seems to be a brain correlate of the behavioral phenomenon induced by antidepressant treatment. In volunteers taking medication, the amygdala response to masked fearful faces was decreased.7 This contrasts with the increased amygdala response seen in people with MDD.

Further support for the hypothesis that treatment can cause emotional blunting comes from data suggesting a dose-response effect, and evidence that emotional blunting can be resolved by lowering the dose of the medication used or its withdrawal.[8]

Considering the pharmacology responsible for emotional blunting, Professor Fagiolini suggested the phenomenon may arise from serotonergic effects on the frontal lobes themselves or inhibitory serotonergic modulation of mid-brain dopamine systems which project to the prefrontal cortex.

Emotional dysfunction an unresolved part of MDD itself

The existence and adverse impact of emotional blunting were acknowledged by Roger McIntyre (University of Toronto, Toronto, Ontario, Canada) who noted that around 30% of people taking medication for MDD report some form of apathy. However, he contended that this may simply reflect the fact that antidepressant agents do not always effectively treat the emotional dysfunction component inherent in MDD.[2]

> Association with medication does not mean causal connection

Evidence from close to 4,000 participants enrolled in the STAR*D study showed that low mood and loss of interest were major features of depression from the outset.9 Along with cognitive disturbance, depressed mood and experience of decreased reward accounted for half the impairment seen in psychosocial function.[9]

Professor McIntyre also cited evidence that anhedonia is present in around 75% of people with MDD, is associated with poor prognosis and suboptimal treatment response, and may relate to disturbances of central dopaminergic, mesolimbic and mesocortical reward pathways.[10-13]

While there is clinical trial evidence that antidepressant treatment improves emotional blunting present at baseline,[2,14] resolution of this dimension of depression is often incomplete. There was consensus that achieving full functional recovery – in addition to resolving symptoms – means targeting all components of depression and this applies to emotional dysfunction as much as to the cognitive and physical burden of MDD.

1. Boyce PM. Med Today 2015;16:67-69
2. Goodwin GM et al. J Affect Disord 2017;221:31-35
3. Rosenblat JD et al J. Affect Disord 2019;243:116-120
4. Price J et al. Br J Psychiatry 2009;195:211-217
5. Price J, Goodwin GM. Medicographia 2009;31:152-156
6. Harmer CJ et al. Am J Psychiatry 2004;161:1256-1263
7. Harmer CJ et al. Br J Psychiatry 2009;195:102-108
8. Sansone RA, Sansone LA. Psychiatry (Edgmont) 2010;7:14-18
9. Fried EI, Nesse RM. PLoS One 2014;9:e90311
10. Cao B et al. Front Psychiatry 2019;10:17
11. Franken IH et al. J Affect Disord 2007;99:83-89
12. Pan Z et al. Curr Pharm Des 2017;23:2065-2072
13. Buckner JD et al. Psychiatry Res 2008;159:25-30
14. Corruble E et al. Int J Neuropsychopharmacol 2013;16:2219-2234

Depression

Long-acting injectables together with medical team training may facilitate functional recovery

Early use of long-acting injectables together with targeted staff training may facilitate short- and long-term functional recovery in patients with early-phase schizophrenia. Charlotte Emborg Mafi (OPUS Clinic, Aarhus University Hospital, Denmark) shared clinical insights and highlighted the importance of staff education for overcoming treatment barriers.

We need to pay more attention to functional recovery, said Dr Emborg during her presentation at EPA Virtual 2021. Maximizing health-related quality of life and attaining personal treatment goals are important treatment objectives for patients with schizophrenia,[1-3] and for this we need to tailor treatment to the individual.

> Focus on functional recovery

Non-adherence to medication is a significant issue in schizophrenia, and for patients who do not adhere to their treatment, the risk of relapse is almost five times higher five years after initial recovery compared to those who do adhere.[4,5]

New evidence confirms early LAIs reduce hospitalization

In a recently published study, use of a long-acting injectable (LAI) was shown to dramatically delay the time to first hospitalization and reduce the incidence rate of first hospitalization in patients with early-phase schizophrenia and first-episode psychosis.6

In the trial, conducted in a real-world clinical setting, study sites were randomized to encourage the use of an LAI (19 sites) or to continue with clinician's choice of usual care (20 sites), which may or may not have included LAIs.[6]

At sites randomized to encourage use of the LAI, the incidence rate of first hospitalization was reduced by 44%, with a 15% absolute reduction in risk of hospitalization at 2-year follow-up, compared with those using usual care.[6]

> LAIs are a natural part of the treatment package

We know that relapse can jeopardise patient functioning.[7] Maintenance treatment with LAIs should not be reserved for patients later in the disease process, said Dr Emborg. For patients in whom maintenance treatment is indicated, second-generation LAIs should be proposed early to improve outcomes, including in younger patients – and this will translate into less relapse and fewer hospital stays.

> Maintenance treatment with LAIs should not be reserved for patients later in the disease process

Optimal treatment can only be achieved with well-trained staff

In the aforementioned study, clinicians at sites that encouraged LAI use underwent a specific training program that included education on the role of non-adherence in relapse and hospitalization, the principles of shared decision-making, communication strategies, role-playing and ways to overcome logistical barriers to the use of LAI across different healthcare settings.[6]

> Team training is key to offering the best possible treatment

Only 14% of patients at these sites did not accept the study because they did not want to use an LAI, highlighted Dr Emborg.[6] So, training of the team is key to providing the best possible treatment to patients.

> Barriers to use of LAIs often do not come from patients or caregivers, but from the clinicians themselves

1. Hasan et al. World J Biol Psychiatry 2013;14:2–44
2. Lehman et al. APA practice guideline for the treatment of patients with schizophrenia. 2nd edition, 2010
3. NICE Guidance 2014. Available from: https://www.nice.org.uk/guidance/cg1781
4. Robinson et al. Arch Gen Psychiatry 1999;56:241–247
5. Caseiro et al. J Psychiatr Res 2012;46:1099–1105
6. Kane et al. JAMA Psychiatry 2020;77:1217–1224
7. Emsley et al. Schizophr Res 2013;148:117–121

Dr Emborg pointed out that barriers to use of LAIs often do not come from patients or caregivers, but from the clinicians themselves. Actively involving patients in treatment decisions is key to successful outcomes, she said, and training should be given to every staff member with patient contact, not only the psychiatrist and nurse.

Tailored treatment can only be offered by a well-trained staff..

Depression, Bipolar & Schizophrenia

Partial dopamine agonists: wide spectrum of activity and indications

Early use of long-acting injectables together with targeted staff training may facilitate short- and long-term functional recovery in patients with early-phase schizophrenia. Charlotte Emborg Mafi (OPUS Clinic, Aarhus University Hospital, Denmark) shared clinical insights and highlighted the importance of staff education for overcoming treatment barriers.

In the mesolimbic pathway, which is thought to be hyperactive in people with positive symptoms, dopamine partial agonist binding to postsynaptic D2 receptors is associated with improvement in mania and psychosis.[1-3] In this setting, the partial agonists act functionally as antagonists by displacing excess dopamine from receptor sites.

In the mesocortical pathway, which is thought to be hypoactive in people with negative and cognitive symptoms, the postsynaptic binding of dopamine partial agonists again brings therapeutic benefit.[1,2]

But this seems to be because the partial agonists enhance dopamine transmission if the endogenous transmitter is present in abnormally low concentrations, Pierre Blier (University of Ottawa, Canada) told CINP 2021 Virtual.

Modulation holds the key

This modulating effect contrasts with the pharmacological antagonists, which consistently reduce dopamine transmission with receptor occupancy of around 60% and above.

> Partial agonists turn the dial down in a hyperdopaminergic environment but have the opposite effect when endogenous dopamine is deficient

It is also important in tolerability: because of their intrinsic activity, the partial agonists activate dopamine receptors to some extent, reducing the likelihood of adverse side effects.

Similar but different

All the dopamine partial agonists in clinical use bind with high affinity and have intrinsic activity at the D2 receptor, but they have distinct pharmacological profiles at monoamine receptors, Professor Blier said. Key factors to consider are:

- The extent of 5-HT2A antagonism, which reduces extrapyramidal symptoms. Having greater antagonistic activity at 5-HT2A than activity at the D2 receptor decreases motor side effects.
- Agonism at the 5-HT1A receptor may have beneficial therapeutic effects.
- Antagonism at the α2-adrenoceptor may attenuate negative symptoms
- Antagonism at the α1-adrenoceptor may attenuate extrapyramidal symptoms.

Functional connectivity is also important. Output to the forebrain is governed by interactions between monoamine receptors, and blockade of norepinephrine (NE) α2C receptors on NE and serotonin terminals enhances NE and serotonin release, he continued.

> The partial agonists' activity at serotonin and adrenergic receptors is also relevant to their therapeutic effects

Clinical insights

Controlled studies and experience suggest that the dose range to be used in depression should be lower than the dose range needed in mania and psychosis, when more drug is required to significantly displace excess endogenous dopamine.

Indeed, said Professor Blier, there is little or no overlap between the therapeutic dose range of dopamine partial agonists in these different settings.

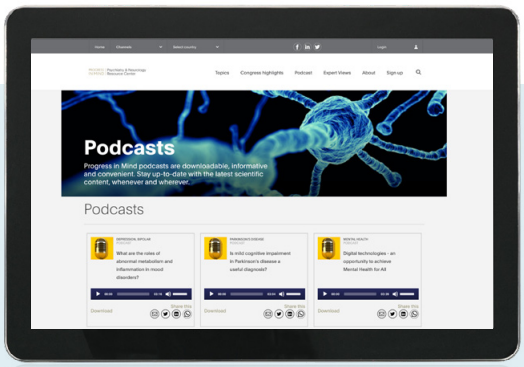
The practical clinical context was taken up later in the same session by Steven Potkin (University of California Irvine, USA) who emphasized that, in schizophrenia, non-adherence with antipsychotic medication is frequent and associated with poor outcome, while early and sustained treatment is associated with better outcome.[5]

1. Abi-Dargham A, Moore H. Neuroscientist 2003;9:404-16
2. Lieberman JA. CNS Drugs 2004;18:251-67
3. Tamminga CA, Carlsson A. Curr Drug Targets Neurol Disord 2002;1:141-9
4. Stahl's Essential Psychopharmacology 4th edition (online version)
5. Fleischhacker WW et a. Neuropsychopharmacology 2014;39:S375

PROGRESS IN MIND | Psychiatry & Neurology Resource Center

This magazine gives you a flavor of the content you will find in Progress in Mind Psychiatry & Neurology Resource Center, a website delivering the latest news, views and insights relating to a variety of topics within psychiatry and neurology.

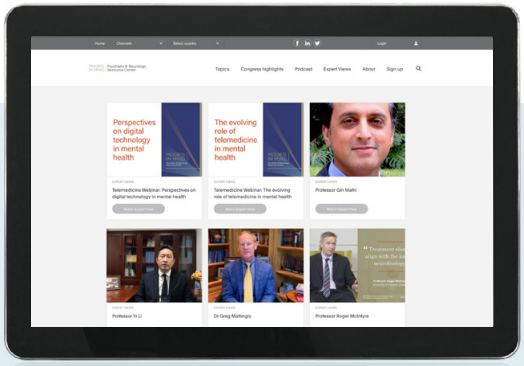
Progress in Mind Resource Center also features the Lundbeck Institute Campus – offering exclusive Lundbeck Institute content and resources including image banks and slide decks to use for your learning and teaching needs.



Podcasts

Progress in Mind podcasts are downloadable, informative and convenient. Stay up-to-date with the latest scientific content, whenever and wherever.

progress.im/en/podcast



Expert Views

Covering a multitude of subjects across psychiatry and neurology, our 'Expert Views' shares topical content from experts in brain health.

progress.im/en/content/expert-views

Brought to you by Lundbeck