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Acta Medica Marisiensis 2014;60(2):61-66 DOI: 10.2478/amma-2014-0014

RESEARCH ARTICLE

Augmentation Strategies for Patients with Major Depressive Disorder with an Inadequate Response to Antidepressant Monotherapy

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Introduction: Major depressive disorder is a chronic and debilitating disease characterized by a wide range of emotional and physical symptoms that coexist during a depressive episode and may reoccur at some point during the progression of the disease for the majority of patients. The purpose of the study was to investigate psychiatrists' experience regarding the response to antidepressive treatment and their options regarding augmentation strategies in depression with incomplete response to antidepressant monotherapy.
Method: We applied an 18-item questionnaire containing multiple choice questions to adult psychiatrists working in ambulatories, hospitals or mental health centers.
Results: Fourty-two psychiatrists have agreed to answer the questionnaire. The majority of them were psychiatry specialists, between 35 and 49 years of age, working in an outpatient unit. For the majority of doctors, SSRIs (Serotonin Reuptake Inhibitors) proved to be the first line treatment both for the first depressive episode and for recurrent depression, followed by SNRI (Serotonin and Noradrenalin Reuptake Inhibitors). Regarding the duration of maintenance treatment for the patients who achieved complete remission after the first episode of depression, the results showed a wide spectrum from 4 to 9 months.
Conclusions: Incomplete response to antidepressive monotherapy is very frequent both for the first depressive episode and for recurrent depression. Given the pharmacological profile that some atypical antipsychotic have, augmentation with atypical antipsychotics in patients with inadequate response to antidepressant monotherapy is a useful therapeutic strategy that should be considered.

Keywords: depression, augmentation, incomplete response

Received: 11 June 2013 / Accepted: 9 April 2014

Introduction

Major Depressive Disorder (MDD) is a chronic and debilitating disease, characterized by a wide range of emotional and physical symptoms that can coexist during a depressive episode and may reoccur at some point in the evolution of the disease. It is considered that by 2020 depression will be the second leading cause of morbidity worldwide after cardiovascular disease. For patients with a major depressive episode, the possibility of experiencing another episode at some point in the future is 85% [1]. Remission rates after the first antidepressant treatment are small (less than 30%) and incomplete or suboptimal response is frequently encountered [2].

Strategies adopted for patients with incomplete response to antidepressant treatment may include: optimizing the dose, switching to another antidepressant, combinations of antidepressants, augmentation with carbamazepine, lithium, buspirone, thyroid hormones or an atypical antipsychotic, pharmacotherapy combined with psychotherapy, deprivation of sleep, light therapy, electroconvulsive therapy (ECT), vagus nerve stimulation, transcranial magnetic stimulation and deep brain stimulation [3,4].

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Our study aims to assess the experience of psychiatrists about patients with incomplete response to antidepressant monotherapy.

Objectives

- Demonstration of increased frequency of incomplete response to antidepressant monotherapy;
- Evidence that the SSRIs and SNRIs are the most commonly used classes of antidepressants as for the first episode depression, recurrent depression;
- Evidence that augmentation with atypical antipsychotics is the preferred method of psychiatrists compared to other treatment options for depression with incomplete response to antidepressant monotherapy.

Methods

Evaluation of therapeutic options of psychiatrists was based on a questionnaire with 18 items (presented at the end of this paper), designed by team members. The questionnaire comprises 18 multiple-choice questions addressed to specialized outpatient psychiatrists, hospitals or mental health centres. After general questions related to age, employment, vocational training and seniority, there is a set of questions about treatment options for the first

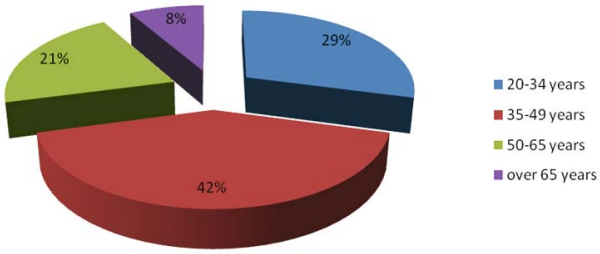

Fig. 1. Age distribution of psychiatrists who answered the questionnaire

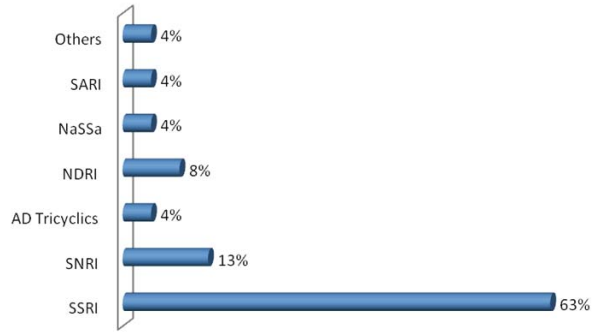

Fig. 2. Therapeutic option in the first depressive episode as first-line therapy

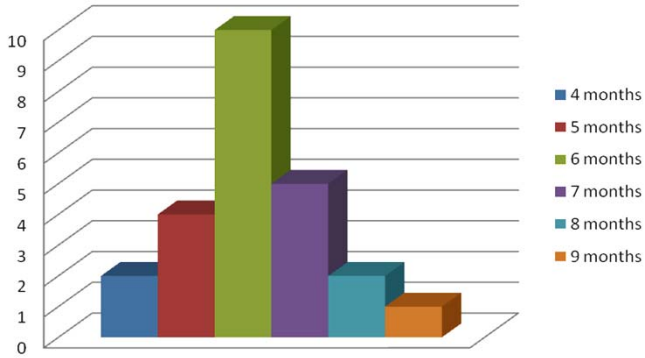

Fig. 3. The duration of maintenance treatment in patients who archived complete remission

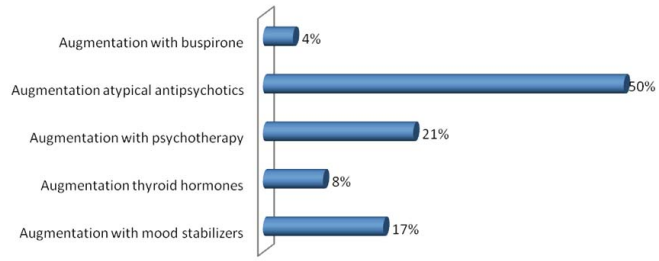

Fig. 3. The duration of maintenance treatment in patients who archived complete remission

depressive episode and for recurrent depressive episodes. The last question concerns the effectiveness of atypical antipsychotics used as augmentation therapy in depression, with incomplete response to antidepressant monotherapy. For the interpretation of data we used statistical programs SPSS 11 for Windows and GraphPad Prism version 6.

Results

The questionnaire was sent to 60 psychiatrists. Fourty-two of them have agreed to answer the questionnaire, all of them from Mureş county.

The majority of the respondents were psychiatry specialists, between 35 and 49 years of age, working in an outpatient unit (Figure 1).

Regarding the therapeutic option in the first depressive episode as first-line therapy, the responders could choose between the next seven options:

– SSRI – Serotonin Reuptake Inhibitors (paroxetinum, sertralinum, citalopramum, escitalopramum, fluvoxaminum, fluoxetinum);
– SNRI – Serotonin and Noradrenalin Reuptake Inhibitors (venlafaxinum, duloxetinum, milnacipran);
– AD Tricyclics (ampitriptilinum, clomipraminum, doxepinum);
– NDRI – Norepinephrine-dopamine reuptake inhibitors (bupropion);
– NaSSa – Noradrenergic and specific serotonergic antidepressants (mirtazapinum, mianserinum);
– SARI – Serotonin antagonist and reuptake inhibitors (nefazodone, trazodone);
– Others: tianeptinum, agomelatinum.

As shown in Figure 2, for the majority of doctors, SSRIs (Serotonin Reuptake Inhibitors) proved to be the first line treatment for the first depressive episode, followed by SNRI (Serotonin and Noradrenalin Reuptake Inhibitors). No correlation was found between the age of responders and treatment preference.

Regarding the duration of maintenance treatment for the patients who achieved complete remission after the first episode of depression, the results showed a wide spectrum from 4 to 9 months (Figure 3). On average, incomplete response to antidepressive monotherapy was reported to be 25% in case of first depressive episode and 28% for recurrent depression.

As shown in Figure 4, in case of incomplete response, psychiatrists used all available therapeutic strategies, with the mention that augmentation with atypical antipsychotics is the preferred method. Quetiapine, olanzapine and aripiprazole are considered to be the most effective atypical antipsychotics in this case.

Discussions

Incomplete response in depression is always associated with an increased risk of relapse [5,6], a significant impairment in all functions (social, occupational, academic) [7] and an increase in costs associated with the treatment of these patients [8,9].

We need to find new strategies in this case, taking into account the fact that with monotherapy only 1/3 of depressed patients achieve remission. If we think that in 2020 depres-

sion will be the second cause of morbidity after cardiovascular diseases and the guides for the treatment of ischemic cardiopathy, for example, recommend at least 3 drugs from different classes, it should not be a problem to recommend two classes of drugs for a depressed patient, although a large number of psychiatrists do not agree with this.

Our paper demonstrates that augmentation with atypical antipsychotics is the preferred method of augmentation for psychiatrists from Mureș county, compared to other treatment options for depression with incomplete response to antidepressant monotherapy. This is the case regardless if the neuroleptic is already approved or is being used off label. A meta-analysis made by Papakostas et al. in 2007 showed that the response to an antidepressant augmentation with an atypical antipsychotic may be beneficial in patients with treatment-resistant depression [10].

Studies over the past five years have shown the beneficial effect of combining atypical antipsychotics (e.g. aripiprazole or quetiapine), not only in the case of patients with resistant depression, but also in those cases where there is an inadequate response, incomplete to antidepressive monotherapy [11–15]. Currently in Romania only quetiapine is approved for the treatment of depression with incomplete response, as an augmentation strategy to antidepressive monotherapy.

Most drugs with antidepressive effect exercise their effect by inhibiting reuptake of one or more neuromediators: serotonin (5-HT), dopamine (DA), norepinephrine (NE), but also by their function of 5-HT_{2A} receptor antagonists or partial agonists of 5-HT_{1A} autoreceptors. These are also common mechanisms of action for atypical antipsychotics [5].

In the future, we wish to extend our study to the entire country, and also to carry out a comparing study between Romania, France and England regarding the psychiatrist's therapeutic options in depression.

Conclusions

Incomplete response to antidepressive monotherapy is very frequent both for the first depressive episode and for recurrent depression. Given the pharmacological profile that some atypical antipsychotic have, augmentation with atypical antipsychotics in patients with inadequate response to antidepressant monotherapy is a useful therapeutic strategy that should be considered. Since currently there is relatively little data in this area, further clinical studies are needed to assess the risk-benefit of association of antidepressive medication and atypical antipsychotics for depressed patients without psychotic features.

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QUESTIONNAIRE FOR ASSESSMENT OF THERAPEUTIC OPTION IN DEPRESSION

1. In what type of facility do you work?	☐ Specialized outpatient	
	☐ Mental health center	
	☐ Hospital	
2. Your age is in the range:	☐ 20-34 years	☐ 50-65 years
	☐ 35-49 years	☐ over 65 years
3. What is your professional level?	☐ psychiatry resident	
	☐ psychiatry specialist	
	☐ senior specialist in Psychiatry	
4. For how many years have you worked in Psychiatry?	☐ less than 5 years	☐ 10-19 years
	☐ 5-9 years	☐ over 20 years
5. How many patients with major depressive disorder, major depressive episode, single or recurrent, **without psychotic features,** do you see per month and per year, on average?	_____ patients per month _____ patients per year	
6. What is your therapeutic option (in percents) in the **first depressive episode** as first-line therapy? (choose only classes that you use, reported to your total number of patients)		
SSRI (paroxetinum, sertralinum, citalopramum, escitalopramum, fluvoxaminum, fluoxetinum)	_____ %	
SNRI (venlafaxinum, duloxetinum, milnacipran)	_____ %	
AD Tricyclics (ampitriptilinum, clomipraminum, doxepinum)	_____ %	
NDRI (bupropion)	_____ %	
NaSSa (mirtazapinum, mianserinum)	_____ %	
SARI (nefazodone, trazodone)	_____ %	
Others: tianeptinum, agomelatinum	_____ %	
7. How do you assess therapeutic response to antidepressant therapy?	☐ based on clinical symptoms	
	☐ based on psychometric assessments (HAM-D, MADRS, CGI, etc)	
	☐ based on dosing the antidepressant levels in the blood	
8. What is the duration of maintenance treatment in **patients who achieved complete remission?**	_____ months	
9. What is the percentage of patients that **do not achieve remission**, but present only a partial response (or lack of response) to antidepressant monotherapy, **in the first depressive episode?**		
SSRI (paroxetinum, sertralinum, citalopramum, escitalopramum, fluvoxaminum, fluoxetinum)	_____ %	
SNRI (venlafaxinum, duloxetinum, milnacipran)	_____ %	
AD Tricyclics (ampitriptilinum, clomipraminum, doxepinum)	_____ %	
NDRI (bupropion)	_____ %	
NaSSa (mirtazapinum, mianserinum)	_____ %	
SARI (nefazodone, trazodone)	_____ %	
Others: tianeptinum, agomelatinum	_____ %	

10. What is **the duration** of antidepressant treatment administration to be evaluated as an incomplete response or lack of response to antidepressant monotherapy?				
☐ 1 week	☐ 2 weeks	☐ 3 weeks	☐ 4 weeks	☐ 5 weeks

11. In these patients **with incomplete response to antidepressant monotherapy, in the first depressive episode**, what is your preferred therapeutic strategy?	
Dose optimization	_____ %
Changing the antidepressant with another one, from the same class or a different class	_____ %
Combination of two antidepressants	_____ %
An augmentation strategy with mood stabilizers, buspirone, thyroid hormones, psychotherapy, atypical antipsychotics	_____ %
Other, please specify _____	_____ %

12. What is the proportion of patients with an **incomplete response to antidepressant monotherapy, in the first depressive episode,** where you use an augmentation therapy?	
Augmentation with mood stabilizers	_____ %
Augmentation thyroid hormones	_____ %
Augmentation with psychotherapy	_____ %
Augmentation atypical antipsychotics	_____ %
Augmentation with buspirone	_____ %

13. What is your therapeutic option (in percents) **in case of recurrent depression** (choose only classes that you use)?	
SSRI (paroxetinum, sertralinum, citalopramum, escitalopramum, fluvoxaminum, fluoxetinum)	_____ %
SNRI (venlafaxinum, duloxetinum, milnacipran)	_____ %
AD Tricyclics (ampitriptilinum, clomipraminum, doxepinum)	_____ %
NDRI (bupropion)	_____ %
NaSSa (mirtazapinum, mianserinum)	_____ %
SARI (nefazodone, trazodone)	_____ %
Others: tianeptinum, agomelatinum	_____ %

14. What is the percentage of patients that **do not achieve remission**, but present only a partial response (or lack of response) to antidepressant monotherapy, **in case of recurrent depression?**	
SSRI (paroxetinum, sertralinum, citalopramum, escitalopramum, fluvoxaminum, fluoxetinum)	_____ %
SNRI (venlafaxinum, duloxetinum, milnacipran)	_____ %
AD Tricyclics (ampitriptilinum, clomipraminum, doxepinum)	_____ %
NDRI (bupropion)	_____ %
NaSSa (mirtazapinum, mianserinum)	_____ %
SARI (nefazodone, trazodone)	_____ %
Others: tianeptinum, agomelatinum	_____ %

15. In case of patients **with recurrent depression, with incomplete response to antidepressant monotherapy,** what is your preferred therapeutic strategy?	
Dose optimization	_____ %
Changing the antidepressant with another one, from the same class or a different class	_____ %

Combination of two antidepressants	_____ %
An augmentation strategy with mood stabilizers, buspirone, thyroid hormones, psychotherapy, atypical antipsychotics	_____ %
Other, please specify _____	_____ %
16. What is the proportion of patients with an **incomplete response to antidepressant monotherapy, in recurrent depression,** where you use an augmentation therapy?	
Augmentation with mood stabilizers	_____ %
Augmentation thyroid hormones	_____ %
Augmentation with psychotherapy	_____ %
Augmentation atypical antipsychotics	_____ %
Augmentation with buspirone	_____ %

17. Which atypical antipsychotic (approved or off label) do you use for the treatment of **Major Depressive Disorder. Major Depressive Episode, single or recurrent, without psychotic features?**

☐ Quetiapinum	☐ Aripiprazolum	☐ Olanzapinum	☐ Risperidonum	☐ Ziprasidonum

18. Based on your clinical experience, on a scale from 1 (completely ineffective) to 10 (very efficient) please evaluate the effectiveness as an augmentation therapy in **Major Depressive Disorder. Major Depressive Episode, single or recurrent, without psychotic features** for the following atypical antipsychotics:

Quetiapinum _____	Aripiprazolum _____	Olanzapinum _____	Risperidonum _____	Ziprasidonum _____