Non-Interventional Study (NIS) Report

Synopsis

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Retrospective observational study to estimate the Duration of Initial ANtidepressAnt treatment in patients with recurrent depressive disorder who demonstrated a suboptimal response to therapy - DIANA

Study dates:	First subject in: 10 NOV 2013 Last subject out: 31 DEC 2014/

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NIS REPORT SYNOPSIS

Retrospective observational study to estimate the Duration of Initial ANtidepressAnt treatment in patients with recurrent depressive disorder who demonstrated a suboptimal response to therapy - DIANA

Study sites:	15 study sites in Russia
Publications:	---
Study dates:	10 NOV 2013 - 31 DEC 2014
Primary objective:	To evaluate the duration of treatment with an initial antidepressant taken as monotherapy in patients in whom treatment was changed because of suboptimal response at physician's discretion.
Secondary objectives:	1. To evaluate the change to pharmacotherapy strategy following suboptimal response: • Switch – discontinuation of initial antidepressant (AD) and administration of another AD; • Augmentation – Addition of another drug (which is not an AD) to initially administered AD; • Switch from initial AD to another AD with the addition of another drug, which is not an AD (combination of switch and augmentation); • Combined administration of initial AD with another AD;

- Combined administration of the 2 new ADs;
  Discontinue pharmacotherapy;
- Electro-convulsive therapy.

2. To describe pharmacological agents used for augmentation.
3. To describe doses of pharmacological agents used for augmentation.
4. To describe treatment of previous depressive episode by doses of antidepressants used and duration of treatment.
5. To describe maintenance treatment after previous depressive episode by doses of antidepressants used and duration of treatment.
6. To describe the source of the patient's referral to a psychiatrist: (1) psychotherapist; (2) neurologist; (3) internist; (4) physician of other speciality; (5) psychologist; (6) came himself; (7) other; (8) not known.

Methodology:	This is a retrospective observational study. Data were obtained by chart review.
Number of subjects:	Analyzed: 450 subjects (15 study sites)
Main inclusion/exclusion criteria:	Female or male aged between 18 and 65 years (inpatients and outpatients) diagnosed with an episode of major depression relating to RDD (ICD-10, Version 2010) initially treated with a single antidepressant (using a flexible dosage regimen if required) and for whom initial treatment changed because of a suboptimal response at physician's discretion, which is clearly documented in the patient's medical chart. Patients currently participating in any other clinical or non interventional trial, or have completed their participation with the last 30 days were excluded. Patients with current psychiatric or general medical conditions which require concomitant use of lithium, thyroid hormones, or atypical antipsychotics and patients with unstable general medical condition were excluded. Patients who were pregnant or were suspected to be pregnant during the period when a patient had received treatment for MDE (Major Depressive Episode)
Criteria for evaluation:	**Primary:** time between initiation of antidepressant monotherapy and the alteration and/or augmentation of pharmacotherapy as a result of a suboptimal response to initial therapy at physician's discretion. **Secondary variables include:** 1. Distribution of the seven pharmacotherapy strategies following

suboptimal response: (switch; augmentation; combination of switch and augmentation; combined administration of initial AD with another AD; combined administration of the 2 new ADs; discontinuation of pharmacotherapy; electro-convulsive therapy) among the patients population.

2. Rate of the different pharmacological agents prescribed for augmentation; rout of their administration; mean and median duration of courses of treatment.
3. Mean and median doses of pharmacological agents used for augmentation.
4. Mean and median doses of antidepressants used for the treatment of previous depressive episode; mean and median time from administration till discontinuation.
5. Mean and median doses of antidepressants used for the maintenance treatment after previous depressive episode; mean and median time from administration till discontinuation.
6. Distribution of the eight sources of the patient's referral to a psychiatrist (psychotherapist; neurologist; internist; physician of other speciality; psychologist; came himself; other; and not known).

Statistical methods: Descriptive statistics

Results:

1. **Demographic characteristics**

The study population consisted of 115 men and 335 women (total 450) aged 19 – 67. Average age was 41.8 years (SD 13.3 years) for men and 47.3 years (SD 12.2 years) for women.

The patients were enrolled across 15 centres located in 8 cities of 5 federal districts of Russia. The majority of patients (229) were enrolled in the Central federal district, particularly, in Moscow, followed by the Northwestern (n=56) and Volga federal districts (n=50) with minor contribution from the North Caucasian and Southern federal districts.

2. **Baseline disease characteristics**

Most patients (88.4% of women and 84.4% of men) had no comorbid mental disorders.

Only 24.8% of women and 38.3% of men had no comorbid somatic disorders which indicates significant comorbidity, especially for gastro-intestinal diseases, taking into account relatively young average age of participants.

Analysis of disease duration (recurrent depressive disorder, RDD) revealed that approximately every third woman (28.8%) and every third man (29.31%) had RDD diagnosed established for less than a year. Almost all RDD patients have been previously hospitalized.

About 20% of patients have attempted suicide: 9.3% of women and 11.3% of men have the history of 1 attempt, 2.1% of women and 4.4% of men – 2 attempts; 1.5% of women and 0.9% of men – 3 and more attempts.

3. Analysis results

Primary objective:

Median duration of antidepressant (AD) monotherapy for the current depressive episode prior to switch and/or augmentation was 22 days (95% CI: 19, 25) (3 weeks). Data by region shows different duration of AD monotherapy in routine use with the shortest median duration observed in the Central federal district (16 days) while Northwestern and Southern federal districts had 35 and 39 days, respectively (differences between the Central and Northwestern, Central and Southern federal districts are statistically meaningful: no overlapping of confidence intervals).

Average duration of AD therapy for the current depressive disorder before switch and/or augmentation was 38 days (95% CI: 32, 44).

Secondary objectives:

1) Analysis of data by main strategies used when therapeutic response to monotherapy was inadequate shows that switch of one AD with a different AD was the most frequent method: 35% (95% CI: 30.49, 39.29) of all enrolled patients. The second most frequent method was augmentation applied in 20% (95% CI: 16.30, 23.70) of patients. Augmentation was combined with switch similarly frequently: 18% (95% CI: 14.25, 21.31) of patients. Another 9% (95% CI: 6.65, 12.02) of patients underwent augmentation along with combined therapy with two new antidepressants. Thus, augmentation combined with other methods was applied almost in half of the cases (47%). Electroconvulsive therapy (ECT) was the most uncommon strategy used in only two patients (0.44% (95% CI: 0.00, 1.06)).

Table 1. Frequency of various types of pharmacotherapeutic strategies following inadequate therapeutic response

Method	n	Proportion, %	95% CI, %
Switch of AD with a different AD	157	34.89	30.49 .. 39.29
Augmentation	90	20.00	16.30 .. 23.70
Switch combined with augmentation	80	17.78	14.25 .. 21.31
Combined therapy with two new AD	79	17.56	14.04 .. 21.07
Augmentation and combined therapy with two new AD	42	9.33	6.65 .. 12.02
Switch and ECT	2	0.44	0.00 .. 1.06

2) For augmentation pharmacological agents of different therapeutic groups were used. The most-prescribed were antipsychotics: 67% cases (95% CI: 61.63, 72.38) followed by anxiolytics used in 16.67% cases (95% CI: 12.41, 20.93). The third most-prescribed were anticonvulsants used in 10.2% cases (95% CI: 6.74, 13.66). Other pharmacological agents were rarely used.

Median duration of augmentation course was 41 days (95% CI: 32, 49) (i.e. approximately 6 weeks).

Average duration of augmentation course was 470 days (95% CI: 303, 720) which, given the median duration of augmentation course, indicates existence of the patient subgroup taking the drug for the maximum length of time.

3) Comparative analysis of defined daily dose (DDD), adjusted for gender, age and center, showed that most groups used lower dose formulations: average daily dose (ADD) of antipsychotics was 0.5 of average DDD, ADD of anticonvulsants – 0.51 of average DDD, ADD of systemic antihistamines – 0.78 of average DDD. Higher ADD was typical for hypnotics/sedatives and anxiolytics: 28.48 (95% CI: 24.99, 31.96) and 1.36 (95% CI: 0.42, 2.30) of average DDD, respectively.

4) Therapy of the last depressive episode included various AD groups: selective serotonin reuptake inhibitors (SSRI), type A monoamine oxidase inhibitors, non-selective monoamine reuptake inhibitors, etc. The most-prescribed were non-selective monoamine reuptake inhibitors. The second most-prescribed were selective serotonin reuptake inhibitors. Other AD groups and pharmacological agents were used more rarely.

ADD vs. DDD analysis of antidepressants prescribed as therapy of the last depressive episode, adjusted for gender, age and centre, showed that three abovementioned groups of pharmacological agents were used in higher-than-DDD formulations with only type A monoamine oxidase inhibitor ADD being almost equivalent to DDD: 0.98 (95% CI: 0.23, 1.72).

Average AD therapy duration across all subgroups was 99 days (95% CI: 75, 127).

Median AD therapy duration for the last depressive episode was the longest for ‘selective serotonin reuptake inhibitors’ and ‘other antidepressants’ groups: 49 (95% CI: 36, 61) and 49 (23, 70) days, respectively. The shortest average duration and median duration was obtained for type A monoamine oxidase inhibitors: 23 days (95% CI: 22, 41).

5) Of 450 enrolled patients, 156 had indication for maintenance treatment with data was complete for only 71 patients.

As maintenance treatment following groups of pharmacological agents were used: selective serotonin reuptake inhibitors, type A monoamine oxidase inhibitors, non-selective monoamine reuptake inhibitors, other antioxidants, benzamides and diazepines, oxazepines, thiazepines and oxepines. It should be noted that anti-relapse therapy was prescribed for only 1/3 of all patients (34,6 %).

Analysis of ADD vs. DDD adjusted for gender, age and center showed that the highest ADD was reported in selective serotonin reuptake inhibitors group – 1.45 (95% CI: 1.22, 1.69) DDD and the lowest – in benzamides group: 0.10 (95% CI: 0.0, 1.41) DDD. It should be noted that in addition to ADs, other groups of pharmacological agents were sometimes prescribed.

Average duration of maintenance treatment was the longest for ‘non-selective monoamine reuptake inhibitors’ group – 275 days (95% CI: 144, 458) and the shortest for ‘type A monoamine oxidase inhibitors’ group - 11 days (95% CI: 11, 11) (only one observation).

Analysis of median duration of maintenance treatment showed significant data spread: the minimum of 11 days, the maximum of 551 days (95% CI: 13, 1871).

6) In half of the cases the patients visited a psychiatrist on their own – 48.22% of cases (95% CI: 43.61, 52.44). The second most frequent source of referral was the psychotherapist – 20.89% of cases (95% CI: 17.13, 24.64). Neurologists have referred patients to a psychiatrist in 9.11% of cases (95% CI: 6.45, 11.77), physicians – in 5.11% of cases (95% CI: 3.08, 7.15). No distinct difference in the source of referral to a psychiatrist by patient gender was observed.

Adverse events:

No adverse events and/or side effects have been reported during the trial.

4. Summary:

The median duration of treatment with an initial antidepressant taken as monotherapy in patients for whom treatment was changed because of suboptimal response at physician’s discretion was shown to be 22 days (95% ДИ 19; 25), the average duration for this period was 38 days (95% CI: 32, 44). These data vary between regions. Augmentation combined with other methods was applied almost in half of the cases (47%). The most-prescribed agents for augmentation were antipsychotics: 67% cases (95% CI: 61.63, 72.38). The average daily dose of antipsychotics was 0.5 of average DDD. For the therapy of the last depressive episode the most-prescribed agents were non-selective monoamine reuptake inhibitors, which were used in doses higher than DDD and average treatment duration was 99 days (95% CI: 75, 127). Only 34.6% (n=156) patients were assigned for maintenance treatment, the highest ADD was reported in selective serotonin reuptake inhibitors group – 1.45 (95% CI: 1.22, 1.69) DDD and the lowest – in benzamides group: 0.10 (95% CI: 0.0, 1.41) DDD. Average duration of maintenance treatment was the longest for ‘non-selective monoamine reuptake inhibitors’ group – 275 days (95% CI: 144, 458) and the shortest for ‘type A monoamine oxidase inhibitors’ group – 11 days (95% CI: 11, 11) (only one observation). In half of the cases the patients visited psychiatrists by their own – 48.22% of cases (95% CI: 43.61, 52.44).