CNS Spectrums (2017), page 1 of 7. © Cambridge University Press 2017
doi:10.1017/S1092852917000773

ORIGINAL RESEARCH

Is trazodone more effective than clomipramine in major depressed outpatients? A single-blind study with intravenous and oral administration

Massimiliano Buoli, Chiara Rovera, Sara Maria Pozzoli, Alessio Fiorentini, Laura Cremaschi, Alice Caldiroli, and A. Carlo Altamura*

Department of Psychiatry, University of Milan, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milan, Italy

Objective. Some antidepressants, such as trazodone or clomipramine, can be administered intravenously in patients with major depressive disorder (MDD), with potential benefits compared to the standard oral treatment, but available data about their efficacy are limited. The present study was aimed to compare the effectiveness of trazodone and clomipramine (intravenous [i.v.] followed by oral administration).

Methods. Some 42 patients with a diagnosis of MDD according to the DSM–5 were selected and treated with i.v. trazodone or clomipramine according to clinical judgment. The Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale, and the Montgomery-Åsberg Depression Rating Scale were administered at baseline, after 2 weeks, and after 6 weeks, as well as after 1 week of intravenous antidepressant administration. Raters were blinded to type of treatment.

Results. No significant differences were found between treatment groups in terms of effectiveness at endpoint. Borderline statistical significance was found in terms of number of responders in favor of trazodone. In addition, patients treated with trazodone reported fewer total side effects than those treated with clomipramine.

Conclusion. Both i.v. trazodone and clomipramine are rapid and effective options for improving depressive symptoms, although trazodone appears to be tolerated better. Further studies with larger samples and double-blind conditions are warranted to confirm our results.

Received 25 July 2017; Accepted 7 August 2017

Key words: Antidepressant, depression, anxiety/anxiety disorders, clinical trials, mood disorders, pharmacotherapy.

Introduction

Major depressive disorder (MDD) is a prevalent and disabling condition that accounts for high social costs and significant impairment of patients' quality of life and functioning.[1]

It has been estimated that less than 25% of MDD patients receive proper treatment and that up to 20–30% of those adequately treated show residual symptoms and incomplete remission.[2] Given the high frequency of partial/no response to standard antidepressants during a major depressive episode (MDE) (Bauer *et al*, 2013),[3] as well as the poor outcome and high risk of chronicity in patients with a long duration of untreated illness,[4] an early and targeted treatment should be advisable in order to prevent relapses and to improve the prognosis of MDD patients.[5]

The selective serotonin reuptake inhibitors (SSRIs) together with the selective serotonin and noradrenaline reuptake inhibitors (SNRIs) represent the mainstay of the pharmacological interventions, with comparable efficacy but greater tolerability compared to tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs).[6]

However, first-line treatments (SSRIs and SNRIs) for an MDE have some clinical limitations that are represented by no remission in a relevant number of patients (about 50% for SSRIs and SNRIs),[7] delayed effectiveness,[8] and troublesome side effects, including sexual dysfunction,[9] insomnia or sedation,[10] and worsening of anxiety during the first days of treatment.[11]

* Address for correspondence: Alice Caldiroli, Department of Psychiatry, University of Milan, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122, Milan, Italy.
(Email: alyscaldi@gmail.com)

Of note, some antidepressants (citalopram, clomipramine, and trazodone)[12,13] are available as an intravenous formulation, with a potentially more rapid onset of action compared to oral administration.[14–17]

Clomipramine is the most selective serotonergic molecule among the tricyclic antidepressants, with a weak noradrenergic action due to its hepatic metabolite (desmethylclomipramine).[18] Some open-label studies have documented the effectiveness of i.v. clomipramine in improving the symptoms of patients affected by MDD.[19–21] Similar results have been reported with pulse-loading regimens of clomipramine in two samples of depressed adolescents.[22,23] Finally, a more recent randomized placebo-controlled study reported the effectiveness of augmentative low-dose i.v. clomipramine in improving symptoms of patients with an MDE, although low-dose i.v. citalopram was found to be more incisive on anxiety and somatization.[12]

Trazodone performs its pharmacodynamic action as a 2A and 2C serotonin receptor (5-HT_{2A} and 5-HT_{2C}) antagonist and as a serotonin reuptake inhibitor. For these reasons, it belongs to the pharmacological class of serotonin antagonist and reuptake inhibitors.[24] With regard to side effects, the combined action of trazodone allows one to obtain an antidepressant effect while avoiding the unpleasant side effects of SSRIs (e.g., sexual dysfunction) mainly due to binding to the 5-HT_{2A} and 5-HT_{2C} receptors.[25] In addition, the antihistamine properties of trazodone may be particularly advantageous for depressed patients with severe insomnia.[26,27]

Numerous randomized and controlled studies have demonstrated the efficacy of oral trazodone in patients with MDD.[26,28] Furthermore, some of the available clinical data regard samples with elderly depressed patients.[29–34] In contrast, i.v. trazodone, which has been scarcely studied, showed its efficacy in improving depressive symptoms in a small sample of organic depressed patients,[35] whereas Berzewski (1988)[36] reported positive results in an open trial with high doses of i.v. trazodone. In addition, until now, no studies have compared i.v. trazodone with other i.v. antidepressants in terms of efficacy in MDD patients.

Trazodone and clomipramine are two antidepressants with intravenous formulations. Clomipramine is a more selective inhibitor for the serotonin transporter, especially when administered intravenously, whereas trazodone has the additional properties of antagonizing the binding of serotonin to the 5-HT_{2A} and 5-HT_{2C} receptors. The choice to start with an intravenous formulation is supported by the fact that intravenous antidepressants are thought to have a faster onset of efficacy than oral compounds.[16]

For these reasons, the purpose of the present paper was to compare the effectiveness of i.v. trazodone versus clomipramine in the acute treatment of MDD and to evaluate the maintenance of clinical response during a follow-up period with the oral formulations of these compounds.

Methods

Sample

A total of 42 patients (13 males and 29 females) were recruited at the outpatient service (Day Hospital for Mood Disorders) affiliated with the Department of Psychiatry at the University of Milan.

Patients had to be older than 18 years of age, have a diagnosis of MDD, and a current MDE according to the DSM–5[37] to be included in our study.

The exclusion criteria included:

1. resistant depression, defined as a history of no response to at least two antidepressants from different classes, administered for an adequate period of time and at adequate doses[38]
2. pregnancy, breastfeeding, and postpartum also for the effects of hormone fluctuations on mood
3. comorbid medical conditions influencing the severity of depressive symptoms and treatment response (e.g., hypothyroidism or dementia)
4. medical therapies that could modify pharmacokinetics markedly (e.g., antiretrovirals) or cause depression (e.g., corticosteroids)
5. psychiatric comorbidity with the exclusion of substance misuse

In addition, the patients must have discontinued any prior pharmacotherapy for at least 2 weeks.

All included subjects were visited, treated, and followed up after giving their written informed consent and after receiving a full explanation of the study protocol, which had been previously approved by the local ethical committee.

Treatment schedule

In the first phase, patients were assigned to i.v. trazodone (25–100 mg in 250 mL of saline) or clomipramine (25–75 mg in 250 mL of saline) for 1 week according to clinical judgment (type of depressive symptoms, insomnia or anxiety, somatization vs. melancholic features, medical comorbidities, tolerability of side effects). The infusion started in the morning and lasted approximately 1.5 hours for the two treatment groups. Dosages of intravenous treatment were decided according to the severity of depressive symptoms.

Finally, the second phase of the protocol involved shifting to oral administration of the extended-release trazodone (150–300 mg/day) or clomipramine (50–225 mg/day) for 4 weeks.

Intravenous trazodone was substituted with the oral extended-release formulation (150–300 mg per day). This novel formulation (Contramid®) was recently developed and commercialized in the United States and Europe.[39] The extended-release tablets are administered once a day, ensuring maintenance of appropriate levels of drug concentration and better tolerability. Furthermore, this formulation allowed for administration once a day, encouraging better compliance.[39]

Of note, i.v. trazodone is a formulation available only in Italy.

Psychometric scales were performed at baseline (T0), after 2 weeks (T1), and after 6 weeks (T2), as well as after 1 week of intravenous antidepressant administration (T1/2). Patients did not receive any additional medication aside from the trazodone or clomipramine.

Assessment

The raters were blinded with respect to the pharmacological treatment prescribed to each patient. All the raters were trained in clinical scale administration, and they achieved good interrater reliability. In addition, the raters had received specific training for administration of the rating scales.

The Hamilton Depression Rating Scale (HAM–D),[40] the Montgomery–Åsberg Depression Rating Scale (MADRS),[41] and the Hamilton Anxiety Rating Scale (HAM–A)[42] were administered by raters blinded as to the treatment administered to each patient at baseline (T0), after 1 week (T1/2), after 2 weeks (T1), and at 6 weeks (T2). Physical examination was performed. In addition, electrocardiogram and basic laboratory tests were prescribed to all subjects to exclude potential contraindications to intravenous treatment.

The main demographic and clinical variables of the sample were collected: age, gender, duration of untreated illness, number of previous depressive episodes, seasonality, family history of psychiatric disorders in first-degree relatives, number of suicide attempts, number of hospitalizations, lifetime history of psychotic symptoms, presence of atypical symptoms, lifetime substance abuse, type of abuse, and rate of responders/remitters at the end of the protocol.

Safety and tolerability were assessed at each visit after baseline, considering spontaneously reported side effects.

Treatment response was defined by a reduction ≥50% in HAM–D total score, whereas full remission was defined by a score on the HAM–D <8.[43]

Statistical analysis

Descriptive analyses of the subgroups divided according to received antidepressant were performed.

The two treatment groups were compared in terms of demographic and clinical variables, using multivariate analysis of variance (MANOVA) for continuous variables and the χ^2 test for categorical ones.

In order to assess the effect of time, treatment, and time-by-treatment in the two groups of patients divided according to assigned antidepressant, repeated-measures analyses of variance (ANOVAs) (T0–T2) was performed. In addition, a further repeated-measure ANOVA was performed to compare the effectiveness of the two antidepressant treatments after the first week of intravenous administration (T0–T1/2).

For all the analyses, the level of statistical significance was set at 0.05. All statistical analyses were performed using SPSS (v. 23.0, SPSS Inc., Chicago, Illinois).

Results

The sample included a total of 42 subjects (13 males and 29 females): 26 patients were treated with i.v. and oral trazodone and 16 with i.v. and oral clomipramine. The sample size was considered adequate, hypothesizing a confidence interval of continuous variables of 15 and an original population of 300 subjects. In this case, a sample of 37 is sufficient to have reliable results.[44] Trazodone has been administered at mean doses of 44.23 (±10.96) mg i.v. and 161.54 (±67.40) mg orally. Clomipramine has been administered at mean doses of 29.69 (±9.30) mg i.v. and 98.44 (±59.92) mg orally. For each patient, i.v. and oral doses were not changed for the duration of the protocol. The demographic and clinical variables of the two treatment groups are summarized in Table 1.

The groups were not significantly different in terms of seasonality ($\chi^2 = 4.46$, $df = 2$, $p = 0.107$); family history of psychiatric disorders ($\chi^2 = 2.930$, $df = 5$, $p = 0.711$); number of suicide attempters ($\chi^2 = 1.438$, $df = 1$, $p = 0.487$); presence of atypical symptoms ($\chi^2 = 2.001$, $df = 1$, $p = 0.157$); lifetime substance abuse ($\chi^2 = 2.569$, $df = 1$, $p = 0.109$); kind of substance abuse ($\chi^2 = 6.635$, $df = 4$, $p = 0.156$); age ($F = 1.215$, $p = 0.284$); number of previous depressive episodes ($F = 0.067$, $df = 1$, $p = 0.798$); duration of untreated illness ($F = 0.001$, $p = 0.973$); number of hospitalizations ($F = 0.019$, $p = 0.891$), HAM–D baseline total scores ($F = 2.66$, $p = 0.11$); HAM–A baseline total scores ($F = 0.06$, $p = 0.82$); and MADRS baseline total scores ($F = 2.02$, $p = 0.16$).

A statistically significant difference was found between the two treatment groups in terms of gender ($\chi^2 = 4.118$, $df = 1$, $p = 0.042$) and presence of lifetime psychotic symptoms ($\chi^2 = 5.058$, $df = 1$, $p = 0.025$). In particular, the clomipramine group included significantly more females than males with respect to the trazodone group ($p < 0.05$), and lifetime psychotic symptoms were significantly more

TABLE 1. Demographic and clinical variables of the two subgroups of patients divided according to treatment

Variables	Trazodone ($n=26$)	Clomipramine ($n=16$)	p
Gender			
Male	11 (42.3%)	2 (12.5%)	**0.04**
Female	15 (57.7%)	14 (87.5%)	
Age, years	56.46 (±17.2)	48.25 (±15.5)	0.28
Number of previous depressive episodes	4.38 (±4.44)	4.88 (±3.8)	0.80
Family history of psychiatric disorders			
None	16 (61.5%)	8 (50.0%)	0.71
MDD	6 (23.2%)	4 (25.0%)	
BD	1 (3.8%)	1 (6.2%)	
Suicide (not due to definite disorder)	2 (7.7%)	2 (12.6%)	
Schizophrenia	0	1 (6.2%)	
Others	1 (3.8%)	0 (0.0%)	
Duration of untreated illness (years)	6.00 (±8.6)	6.13 (±6.9)	0.97
Suicide attempters			
Yes	3 (11.5%)	1 (6.2%)	0.49
No	23 (89.5%)	15 (93.8%)	
Number of hospitalizations	1.0 (±1.3)	1.13 (±2.8)	0.89
Atypical symptoms			
Yes	4 (15.4%)	6 (37.5%)	0.16
No	22 (84.6%)	10 (62.5%)	
Lifetime substance abuse			
Yes	13 (50.0%)	4 (25.0%)	0.11
No	13 (50.0%)	12 (75.0%)	
Type of substance abuse			
None	13 (50.0%)	12 (75.0%)	0.16
Cannabis	4 (15.4%)	0 (0.0%)	
Cocaine	2 (7.7%)	0 (0.0%)	
Alcohol	7 (26.9%)	3 (18.8%)	
Other	0 (0.0%)	1 (6.2%)	
Lifetime psychotic symptoms			
Yes	0 (0.0%)	3 (18.7%)	**0.03**
No	26 (100.0%)	13 (81.3%)	
Seasonality			
None	23 (88.5%)	10 (62.5%)	0.11
Spring/autumn	3 (11.5%)	5 (31.2%)	
Summer/winter	0 (0.0%)	1 (6.3%)	
Responders			
Yes	12 (46.1%)	3 (18.8%)	0.06
No	14 (53.9%)	13 (81.2%)	
Remitters			
Yes	9 (34.6%)	2 (12.5%)	0.24
No	17 (65.4%)	14 (87.5%)	
Side effects			
None	22 (84.7%)	7 (43.7%)	**0.02**
Sedation	2 (7.7%)	1 (6.3%)	>0.05
Xerostomia	0 (0.0%)	6 (23.1%)	**<0.05**
Skin rash	1 (3.8%)	0 (0.0%)	>0.05
Headache	0 (0.0%)	1 (6.3%)	>0.05
Dizziness	1 (3.8%)	1 (6.3%)	>0.05

Statistically significant differences in bold type. For continuous variables, standard deviations are reported in brackets. BD = bipolar disorder; MDD = major depressive disorder.

common in patients treated with clomipramine than in those treated with trazodone ($p<0.05$).

At endpoint, both two treatment groups showed a significant improvement in HAM–D total scores over time, but no differences were found between the two antidepressants (time effect $F=123.919$ [$p<0.001$]; treatment effect $F=1.614$ [$p=0.213$]; time-by-treatment effect $F=0.001$ [$p=0.974$]). The same results were found for HAM–A (time effect $F=87.968$ [$p<0.001$]; treatment effect $F=0.010$ [$p=0.922$]; time-by-treatment

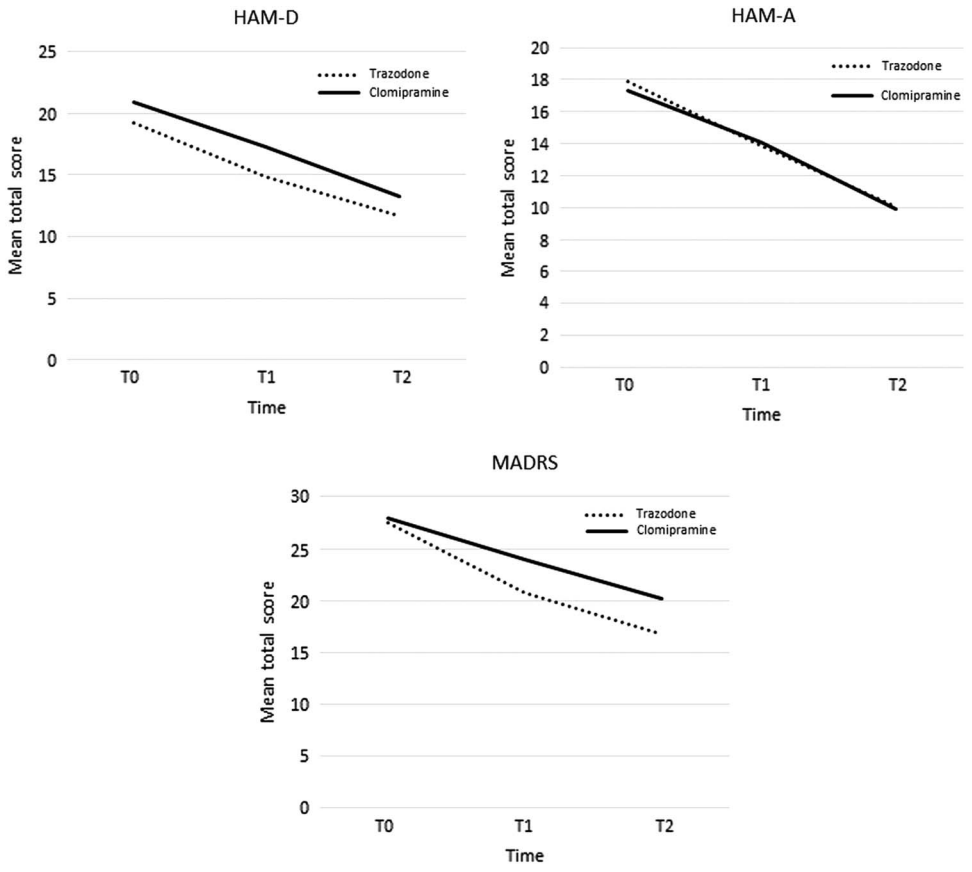

FIGURE 1. Mean total scores change of the psychometric scales over time in the two treatment groups. HAM–A: Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale. Statistics: HAM–D time effect ($F = 123.919$, $p < 0.001$); treatment effect ($F = 1.614$, $p = 0.213$); time-by-treatment effect ($F = 0.001$, $p = 0.974$). HAM–A time effect ($F = 87.968$, $p < 0.001$); treatment effect ($F = 0.010$, $p = 0.922$); time-by-treatment effect ($F = 0.069$, $p = 0.795$). MADRS time effect ($F = 92.702$, $p < 0.001$); treatment effect ($F = 1.064$, $p = 0.310$); time-by-treatment effect ($F = 2.499$, $p = 0.124$).

effect $F = 0.069$ [$p = 0.795$]); and MADRS scores (time effect $F = 92.702$ [$p < 0.001$]; treatment effect $F = 1.064$ [$p = 0.310$]; time-by-treatment effect $F = 2.499$ [$p = 0.124$]) (Figure 1). Of note, no differences on total scores of rating scales were found between the two treatment groups after the first week of i.v. treatment [HAM–D (treatment effect: $F = 2.29$, $p = 0.14$); HAM–A (treatment effect: $F = 0.011$, $p = 0.97$); MADRS (treatment effect: $F = 1.6$, $p = 0.21$)]. In contrast, an early improvement in terms of symptoms was found for both treatment groups (after one week of i.v. treatment for all rating scales: time effect $p < 0.001$).

At endpoint, 46.1% of patients in the trazodone group responded to the treatment, while the responder rate was 18.8% in the clomipramine group ($\chi^2 = 8.39$, $df = 1$, $p = 0.06$); the remitters were 34.6% of patients treated with trazodone and 12.5% of patients treated with clomipramine ($\chi^2 = 6.04$, $df = 1$, $p = 0.24$).

During the treatment period, side effects were reported by 15.4% of patients in the trazodone group and by 56.3% of patients in the clomipramine group, though none of them discontinued the treatment because of serious adverse events ($\chi^2 = 26.74$, $df = 1$, $p = 0.02$). In particular, in the trazodone group, the following side effects were observed: sedation (7.7%), rash (3.8%), and dizziness (3.8%). In the clomipramine group, the most common side effects were xerostomia (23.1%), sedation (6.3%), headache (6.3%), and dizziness (6.3%). Of note, xerostomia was found to be significantly more frequent in the clomipramine group than in trazodone patients ($p < 0.05$).

Discussion

The main result of the present study was the absence of statistically significant differences between trazodone and clomipramine on mean total rating scale scores over time, although both drugs demonstrated improved symptoms in major depressed subjects. Intravenous trazodone and clomipramine, followed by oral

maintenance, therefore seem both to be valid options for the acute treatment of MDD. A borderline significant difference was found with regard to rate of responders in favor of trazodone. This phenomenon may be due to the specific pharmacodynamic properties of trazodone (e.g., 5-HT_{2A} antagonism and the related dopamine release in the frontal cortex)[24] or to baseline major symptom severity of patients in the clomipramine group. Of note, patients in the clomipramine group presented more frequently with lifetime psychotic symptoms, although there were no differences in mean baseline rating scale scores. In addition, global rates of remitters and responders are lower than those reported in the literature, perhaps as a result of the major symptom severity of included outpatients (Day Hospital Unit).[45]

This finding is a bit surprising given the reputation of these compounds, where trazodone is often considered a "weak" antidepressant and more frequently used as a hypnotic. It may also mean that trazodone, often neglected as a full-dose antidepressant, should be more often considered as such.

Trazodone was more tolerated than clomipramine. The clomipramine group presented more frequent xerostomia, which is a troublesome side effect that potentially affects patients' quality of life.[46]

Whether i.v. administration ensures a more rapid onset of action than the oral route is open to debate. In our sample, both treatment groups showed a significant improvement of symptoms only after one week of i.v. treatment. Similarly, a randomized placebo-controlled study demonstrated a speedy efficacy of low-dose i.v. augmentative citalopram in partial/nonresponder MDD patients,[13] and some studies demonstrated a faster action of the i.v. antidepressant treatment compared to the oral route.[16] On the other hand, some authors reported the same efficacy for intravenous pulse loading and oral administration (without more severe side effects) in MDD patients,[21] as also reported in a literature review.[17]

Nevertheless, in clinical practice, i.v. administration presents some advantages. First, it avoids hepatic metabolism, with the consequent achievement of a fast peak plasma concentration and reduced production of metabolites (e.g., desmethylclomipramine), which potentially affect the pharmacodynamic profile of antidepressants.[47] Second, avoiding first-pass metabolism, lower doses are needed to reach the same plasma levels as oral administration.[48] Finally, i.v. administration guarantees treatment compliance.[49]

Some limitations of the present research should be discussed. First, the lack of double-blind and randomized conditions may have biased the results, but the design of the present trial is more adherent to clinical practice. Second, the setting of our study may have influenced the results, as day hospital units usually ensure higher compliance and a stronger therapeutic alliance.[50] Finally, the present paper presents just preliminary results from a small nonrandomized study, one without a placebo control. Further studies with larger samples and double-blind randomized conditions are encouraged to confirm and extend our findings.

Conclusions

Taken as a whole, the results of the present research are preliminary and seem to indicate that trazodone and clomipramine are equally effective in acute treatment of MDD patients, although the first compound is better tolerated, and we demonstrated the utility of short-term intravenous administration of these antidepressants to obtain a more rapid improvement of symptoms.

Disclosures

The authors do not have any conflicts of interest with respect to the contents of the present article. This study was not supported by any pharmaceutical financial interests.

Massimiliano Buoli reports that he has been a Lundbeck consultant.

Chiara Rovera, Sara Maria Pozzoli, Laura Cremaschi, and Alice Caldiroli have nothing to disclose.

Alessio Fiorentini is an Angelini consultant and is also on their speakers bureau.

A. Carlo Altamura has been a Merck and Astra Zeneca consultant and is also on the speakers bureau for Sanofi, Lilly, and Pfizer.

REFERENCES:

1. Wittchen HU, Jacobi F. Size and burden of mental disorders in Europe: a critical review and appraisal of 27 studies. *Eur Neuropsychopharmacol*. 2005; **15**(4): 357–376.
2. Kirino E, Gitoh M. Rapid improvement of depressive symptoms in suicide attempters following treatment with milnacipran and tricyclic antidepressants: a case series. *Neuropsychiatr Dis Treat*. 2011; **7**: 723–728.
3. Bauer M, Pfennig A, Severus E, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. *World J Biol Psychiatry*. 2013; **14**(5): 334–385.
4. Altamura AC, Buoli M, Serati M. Duration of illness and duration of untreated illness in relation to drug response in psychiatric disorders. *Neuropsychiatry*. 2011; **1**: 81–90.
5. Buoli M, Cumerlato Melter C, Caldiroli A, Altamura AC. Are antidepressants equally effective in the long-term treatment of major depressive disorder? *Hum Psychopharmacol*. 2015; **30**(1): 21–27.
6. Chang T, Fava M. The future of psychopharmacology of depression. *J Clin Psychiatry*. 2010; **71**(8): 971–975.
7. Machado M, Iskedjian M, Ruiz I, Einarson TR. Remissions, dropouts, and adverse drugs reactions rates in major depressive

disorder: a meta-analysis of head-to-head trials. *Curr Med Res Opin*. 2006; **22**(9): 1825–1837.
8. Buoli M, Dell'Osso B, Bosi MF, Altamura AC. Slow vs. standard up-titration of paroxetine in the treatment of panic disorder: a prospective randomized trial. *Psychiatry Clin Neurosci*. 2010; **64**(6): 612–619.
9. Dell'Osso B, Buoli M, Baldwin DS, Altamura AC. Serotonin norepinephrine reuptake inhibitors (SNRIs) in anxiety disorders: a comprehensive review of their clinical efficacy. *Hum Psychopharmacol*. 2010; **25**(1): 17–29.
10. Fava M. Daytime sleepiness and insomnia as correlates of depression. *J Clin Psychiatry*. 2004; **65**(Suppl 16): 27–32.
11. Fava M, Hoog SL, Judge RA, Kopp JB, Nilsson ME, Gonzales JS. Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. *J Clin Psychopharmacol*. 2002; **22**(2): 137–147.
12. Altamura AC, Dell'Osso B, Buoli M, Zanoni S, Mundo E. Intravenous augmentative citalopram versus clomipramine in partial/nonresponder depressed patients: a short-term, low dose, randomized, placebo-controlled study. *J Clin Psychopharmacol*. 2008; **28**(4): 406–410.
13. Altamura AC, Dell'Osso B, Buoli M, Bosi M, Mundo E. Short-term intravenous citalopram augmentation in partial/nonresponders with major depression: a randomized placebo-controlled study. *Int Clin Psychopharmacol*. 2008; **23**(4): 198–202.
14. Gastpar M, Ngo Khac T, Gilsdorf U, Baumann P. Comparison of oral and intravenous treatment of depressive states: preliminary results of a WHO collaborative study. *Clin Neuropharmacol*. 1986; **9**(Suppl 4): 434–436.
15. Bareggi SR, Cavallaro R, Pirola R, Altamura AC. Pharmacokinetics and adverse effects of single doses of dothiepin in young and elderly subjects. *Prog Neuropsychopharmacol Biol Psychiatry*. 1990; **14**(2): 163–170.
16. Guelfi JD, Strub N, Loft H. Efficacy of intravenous citalopram compared with oral citalopram for severe depression. Safety and efficacy data from a double-blind, double-dummy trial. *J Affect Disord*. 2000; **58**(3): 201–209.
17. Moukaddam NJ, Hirschfeld RM. Intravenous antidepressants: a review. *Depress Anxiety*. 2004; **19**(1): 1–9.
18. Kelly MW, Myers CW. Clomipramine: a tricyclic antidepressant effective in obsessive compulsive disorder. *DICP*. 1990; **24**(7–8): 739–744.
19. Luscombe DK, Wright J, Jain VK. Plasma level studies of clomipramine and desmethylclomipramine following intravenous infusions of clomipramine in depressive patients. *Postgrad Med J*. 1977; **53**(Suppl 4): 88–96.
20. Dudley DL, Volberding N, Loebel P. Intravenous chlorimipramine and refractory depression. *Gen Hosp Psychiatry*. 1980; **2**(1): 61–64.
21. Pollock BG, Perel JM, Nathan RS, Kupfer DJ. Acute antidepressant effect following pulse loading with intravenous and oral clomipramine. *Arch Gen Psychiatry*. 1989; **46**(1): 29–35.
22. Sallee FR, Pollock BG, Perel JM, Ryan ND, Stiller RL. Intravenous pulse loading of clomipramine in adolescents with depression. *Psychopharmacol Bull*. 1989; **25**(1): 114–118.
23. Sallee FR, Vrindavanam NS, Deas-Nesmith D, Carson SW, Sethuraman G. Pulse intravenous clomipramine for depressed adolescents: double-blind, controlled trial. *Am J Psychiatry*. 1997; **154**(5): 668–673.
24. Stahl SM. Mechanism of action of trazodone: a multifunctional drug. *CNS Spectr*. 2009; **14**(10): 536–546.
25. Khouzam HR. A review of trazodone use in psychiatric and medical conditions. *Postgrad Med*. 2017; **129**(1): 140–148.
26. Fagiolini A, Comandini A, Catena Dell'Osso M, Kasper S. Rediscovering trazodone for the treatment of major depressive disorder. *CNS Drugs*. 2012; **26**(12): 1033–1049.
27. Savarese M, Carnicelli M, Cardinali V, Mogavero MP, Federico F. Subjective hypnotic efficacy of trazodone and mirtazapine in patients with chronic insomnia: a retrospective, comparative study. *Arch Ital Biol*. 2015; **153**(2–3): 231–238.
28. Goracci A, Forgione RN, De Giorgi R, Coluccia A, Cuomo A, Fagiolini A. Practical guidance for prescribing trazodone extended-release in major depression. *Expert Opin Pharmacother*. 2016; **17**(3): 433–441.
29. Gerner R, Estabrook W, Steuer J, Jarvik L. Treatment of geriatric depression with trazodone, imipramine, and placebo: a double-blind study. *J Clin Psychiatry*. 1980; **41**(6): 216–220.
30. Altamura AC, Mauri MC, Colacurcio F, *et al*. Trazodone in late life depressive states: a double-blind multicenter study versus amitriptyline and mianserin. *Psychopharmacology (Berl)*. 1988; **95**(Suppl): 34–36.
31. Altamura AC, Mauri MC, Rudas N, *et al*. Clinical activity and tolerability of trazodone, mianserin, and amitriptyline in elderly subjects with major depression: a controlled multicenter trial. *Clin Neuropharmacol*. 1989; **12**(Suppl 1): 25–33.
32. Monteleone P, Gnocchi G. Evidence for a linear relationship between plasma trazodone levels and clinical response in depression in the elderly. *Clin Neuropharmacol*. 1990; **13**(Suppl 1): 84989.
33. Altamura AC, Mauri MC, Moro AR. Fluvoxamine: a novel 5-hydroxytryptamine uptake inhibitor: present and future clinical application. In. *Headache and Depression: Serotonin Pathways as a Common Clue*. New York: Raven Press; 1991.
34. Schroeck JL, Ford J, Conway EL, *et al*. Review of safety and efficacy of sleep medicines in older adults. *Clin Ther*. 2016; **38**(11): 2340–2372.
35. Roccatagliata G, Abbruzzese G, Albano C, Cocito L, Gandolfo C. Trazodone by intravenous infusion in depressions secondary to organic disease. *Int Pharmacopsychiatry*. 1977; **12**(2): 72–79.
36. Berzewski H. Clinical experience with antidepressive infusion therapy: trazodone. *Psychopharmacology (Berl)*. 1988; **95**(Suppl): 31–33.
37. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. [DSM–5]. Arlington, VA: American Psychiatric Press; 2013.
38. Wijeratne C, Sachdev P. Treatment-resistant depression: critique of current approaches. *Aust N Z J Psychiatry*. 2008; **42**(9): 751–762.
39. Fagiolini A, Amodeo G, Goracci A, Blardi P. Trazodone Contramid® in clinical practice: personalizing antidepressant intervention [in Italian]. *Riv Psichiatr*. 2016; **51**(4): 123–128.
40. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; **23**: 56.
41. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; **134**: 382–389.
42. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959; **32**(1): 50.
43. Amsterdam JD, Horning M, Nierenberg AA. *Treatment-Resistant Mood Disorders*. Cambridge: Cambridge University Press; 2001.
44. Flight L, Julious SA. Practical guide to sample size calculations: an introduction. *Pharm Stat*. 2016; **15**(1): 68–74.
45. Nil R, Lütolf S, Seifritz E. Residual symptoms and functionality in depressed outpatients: a one-year observational study in Switzerland with escitalopram. *J Affect Disord*. 2016; **197**: 245–250.
46. Greenspan D. Xerostomia: diagnosis and management. *Oncology (Williston Park)*. 1996; **10**(3 Suppl): 7–11.
47. Núñez R, Perel JM. Comparative neurotransmitter reuptake and anticholinergic potencies of the 8-hydroxy metabolites of clomipramine. *Psychopharmacol Bull*. 1995; **31**(2): 217–221.
48. Kasper S, Müller-Spahn F. Intravenous antidepressant treatment: focus on citalopram. *Eur Arch Psychiatry Clin Neurosci*. 2002; **252**(3): 105–109.
49. Bouchard JM, Strub N, Nil R. Citalopram and viloxazine in the treatment of depression by means of slow drop infusion: a double-blind comparative trial. *J Affect Disord*. 1997; **46**(1): 51958.
50. Hosaka T, Aoki T, Watanabe T, Okuyama T, Kurosawa H. General hospital psychiatry from the perspective of medical economics. *Psychiatry Clin Neurosci*. 1999; **53**(4): 449–453.