Tesi doctoral

Receptor 5-HT1A i ISRS: Escurçament de la resposta antidepressiva

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RESEARCH PAPER

Preclinical and clinical characterization of the selective 5-HT$_{1A}$ receptor antagonist DU-125530 for antidepressant treatment

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BACKGROUND AND PURPOSE

The antidepressant efficacy of selective 5-HT reuptake inhibitors (SSRI) and other 5-HT-enhancing drugs is compromised by a negative feedback mechanism involving 5-HT$_{1A}$ autoreceptor activation by the excess 5-HT produced by these drugs in the somatodendritic region of 5-HT neurones. 5-HT$_{1A}$ receptor antagonists augment antidepressant-like effects in rodents by preventing this negative feedback, and the mixed β-adrenoceptor/5-HT$_{1A}$ receptor antagonist pindolol improves clinical antidepressant effects by preferentially interacting with 5-HT$_{1A}$ autoreceptors. However, it is unclear whether 5-HT$_{1A}$ receptor antagonists not discriminating between pre- and post-synaptic 5-HT$_{1A}$ receptors would be clinically effective.

EXPERIMENTAL APPROACH

We characterized the pharmacological properties of the 5-HT$_{1A}$ receptor antagonist DU-125530 using receptor autoradiography, intracerebral microdialysis and electrophysiological recordings. Its capacity to accelerate/enhance the clinical effects of fluoxetine was assessed in a double-blind, randomized, 6 week placebo-controlled trial in 50 patients with major depression (clinicaltrials.gov identifier NCT01119430).

KEY RESULTS

DU-125530 showed equal (low nM) potency to displace agonist and antagonist binding to pre- and post-synaptic 5-HT$_{1A}$ receptors in rat and human brain. It antagonized suppression of 5-hydroxytryptaminergic activity evoked by 8-OH-DPAT and SSRIs *in vivo*. DU-125530 augmented SSRI-induced increases in extracellular 5-HT as effectively as in mice lacking 5-HT$_{1A}$ receptors, indicating a silent, maximal occupancy of pre-synaptic 5-HT$_{1A}$ receptors at the dose used. However, DU-125530 addition to fluoxetine did not accelerate nor augment its antidepressant effects.

CONCLUSIONS AND IMPLICATIONS

DU-125530 is an excellent pre- and post-synaptic 5-HT$_{1A}$ receptor antagonist. However, blockade of post-synaptic 5- HT$_{1A}$ receptors by DU-125530 cancels benefits obtained by enhancing pre-synaptic 5-hydroxytryptaminergic function.

Abbreviations

5-HT, serotonin; CGI, Clinical Global Impression; DR, dorsal raphe nucleus; HDRS-17, Hamilton Depression Rating Scale of 17 items; KO, knockout; LOCF, Last observation-carried- forward; MADRS, Montgomery- Asberg Depression Rating Scale; MDD, major depression diagnosis; mPFC, Medial prefrontal cortex; OC, Observed cases; SERT, 5-HT transporter; SSRI, selective 5-HT reuptake inhibitors; WT, wild type

Introduction

Major depression is a severe psychiatric syndrome with high prevalence and socioeconomic impact (Greenberg *et al.*, 2003; Andlin-Sobocki and Wittchen, 2005; Lopez *et al.*, 2006; World Health Organization, 2008). Most of the prescribed antidepressants, the selective 5-HT reuptake inhibitors (SSRI) and the dual 5-HT and noradrenaline reuptake inhibitors, block physiological reuptake mechanisms in 5-hydroxytryptaminergic axons and thereby they increase extracellular 5-HT concentration in forebrain to activate post-synaptic 5-HT receptors required for clinical effects. However, this process is severely compromised by the simultaneous activation of pre-synaptic 5-HT_{1A} receptors (receptor nomenclature follows Alexander *et al.*, 2011) located somatodendritically on 5-HT neurones (5-HT_{1A} autoreceptors) of the midbrain raphe nuclei (Pazos and Palacios, 1985; Pompeiano *et al.*, 1992). The excess 5-HT produced by reuptake inhibition in midbrain activates 5-HT_{1A} autoreceptors, thereby reducing 5-hydroxytryptaminergic neurone activity and terminal 5-HT release (Bel and Artigas, 1992; Blier and De Montigny, 1994; Romero and Artigas, 1997; Lopez *et al.*, 2006), an effect contrary to that required for therapeutic response.

The limited clinical efficacy of 5-HT-enhancing drugs and their delayed action are partly due to this negative feedback mechanism. Upon chronic treatment, 5-HT_{1A} autoreceptors desensitize, leading to the recovery of 5-hydroxytryptaminergic activity and enhanced 5-HT release (Blier and De Montigny, 1994; Artigas *et al.*, 1996). Hence, pharmacological or genetic suppression of 5-HT_{1A} autoreceptor activity enhances the neurochemical and behavioural effects of SSRI in rodents (Artigas *et al.*, 1996; Romero and Artigas, 1997; Knobelman *et al.*, 2001; Bortolozzi *et al.*, 2004; Richardson-Jones *et al.*, 2010). Moreover, patients with a gene polymorphism leading to high 5-HT_{1A} autoreceptor expression are more susceptible to depression and suicide and respond poorly to antidepressant therapy (Stockmeier *et al.*, 1998; Lemonde *et al.*, 2003; 2004; Neff *et al.*, 2009).

Therefore, 5-HT_{1A} receptor antagonists might be useful to improve antidepressant therapy as they could prevent 5-HT_{1A}-autoreceptor-mediated negative feedback. Hence, the non-selective β-adrenoceptor/5-HT_{1A} receptor antagonist pindolol accelerates and, in some instances, increases the efficacy of SSRIs (Artigas *et al.*, 1994; 2001; Blier and Bergeron, 1995; Perez *et al.*, 1997; Ballesteros and Callado, 2004; Whale *et al.*, 2010). However, its complex pharmacology, including its anti-hypotensive effects, limits it clinical use. Pindolol shows a preferential affinity and occupancy of 5-HT_{1A} autoreceptors compared with post-synaptic 5-HT_{1A} receptors in rodent (Serrats *et al.*, 2004) and human (Martinez *et al.*, 2001) brains. In contrast, the prototypical 5-HT_{1A} receptor antagonist WAY-100635 (not available for human use) interacts equally with pre- and post-synaptic 5-HT_{1A} receptors (Forster *et al.*, 1995; Fletcher *et al.*, 1996). Given the requirement to activate post-synaptic 5-HT_{1A} receptors to achieve antidepressant effects in rodents (Haddjeri *et al.*, 1998; Blier and Ward, 2003), it is unclear whether selective 5-HT_{1A} receptor antagonists with equal potency at pre- and post-synaptic 5-HT_{1A} receptors would be clinically effective. Testing this working hypothesis has not been possible so far due to the lack of 5-HT_{1A} receptor antagonists available for human use.

Table 1

In vitro receptor binding profile of DU-125530 for monoaminergic receptors

Receptor	Affinity (nM)
5-HT_{1A}	0.7
5-HT_{1B}	890
5-HT_{1D}	1200
5-HT_{2A}	240
5-HT_{2C}	750
5-HT_3	1100
α_1-adrenoceptor	6.4
Dopamine D_2	5.2
Dopamine D_3	11

Data taken from Mos *et al.* (1997).

Preliminary data indicate that the 5-HT_{1A} receptor antagonist DU-125530 shows high affinity for 5-HT_{1A}- receptors and ≥10-fold selectivity versus other monoaminergic receptors (Mos *et al.*, 1997) (see also Table 1) and antagonizes behavioural effects induced by 5-HT_{1A} receptor agonists in rodents (Joordens *et al.*, 1998; Olivier *et al.*, 1998). Likewise, it occupies pre- and post-synaptic receptors in human brain, as demonstrated by PET scan studies (Rabiner *et al.*, 2002). However, a full characterization of its pharmacological properties is lacking. Therefore, we carried out a collaborative translational study in which we examined the ability of DU-125530: (i) to interact with pre- and post-synaptic 5-HT_{1A} receptors; and (ii) to accelerate or enhance the antidepressant action of fluoxetine.

Methods

Preclinical studies

Animals. All animal care and experimental procedures followed the European Union regulations (OJ of EC L358/1 18/12/1986) and were approved by the Institutional Animal Care and Use Committee. Male albino Wistar rats (230–300 g; Iffa Credo, Lyon, France; total number used: 69) and C57/Bl6J male mice (10–15 weeks old; Iffa Credo; total number used: 41) were kept in a temperature-controlled environment (12 h light–dark cycle) with food and water provided *ad libitum*. Stereotaxic coordinates (in mm) were taken from bregma and duramater according to the atlas of Paxinos and Watson (1998).

Methods. To examine the ability of DU-125530 to interact with pre- and post-synaptic 5-HT_{1A}R in rodent brain, we used receptor autoradiography, single unit extracellular recordings of 5-hydroxytryptaminergic neurones in the dorsal raphe nucleus and of pyramidal neurones in medial prefrontal cortex as well as microdialysis studies, following standard methods routinely used in our laboratory and reported elsewhere (Romero and Artigas, 1997; Amargos-Bosch *et al.*,

2004; Serrats *et al.*, 2004; Diaz-Mataix *et al.*, 2005). A detailed description can be found in the 'Supplementary Methods' section.

Data treatment. In autoradiographic studies, inhibition curves were statistically analysed using GraphPad Prism software (GraphPad Software Inc., San Diego, CA).

Changes in discharge rate were quantified by averaging the values in the third minute after each drug injection. Drug effects were assessed using Student's *t*-test or one-way repeated-measures ANOVA, as appropriate. Data are expressed as the mean ± SEM. Statistical significance has been set at the 95% confidence level.

Dialysate 5-HT concentrations were measured as fmol per fraction and are expressed in the Figures as percentages of baseline (set to 100%). Statistical analysis was carried out using repeated-measures ANOVA using treatment and time as variables.

Materials. 8-OH-DPAT [8-hydroxy-2-(di-*n*-propylamino) tetralin] was from Sigma-Aldrich (St. Louis, MO). Fluoxetine [*N*-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine] was from Tocris (Bristol, UK). Paroxetine [(3*S*,4*R*)-3-[(2*H*-1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl) piperidine] was generously provided by GSK (London, UK). DU-125530 [2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]butyl]-1,2-benzisothiazol-3(2*H*).-one-1, 1-dioxide] was from Solvay Pharma (Brussels, Belgium). (+/–)WAY-100635 [*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-*N*-(2-pyridinyl)cyclohexanecarboxamide] hydrochloride was from RBI (Natick, MA). Stock solutions were prepared, and aliquots were stored at –20°C. Working solutions were prepared daily by dilution in saline at the appropriate concentrations. Doses are expressed as weight of free bases.

Clinical trial

Patients. Consecutive eligible patients aged 18 to 70, referred by general practitioners of primary care centers or from psychiatric emergency services (Catalonian Public Health Service), were recruited. Inclusion criteria were as follows: diagnosis of unipolar major depression using DSM-IV criteria with moderate to severe symptoms (≥18 on the Hamilton Depression Rating Scale of 17 items, HDRS-17). There was a wash-out of 1 week of any antidepressant drug (except for fluoxetine, 28 days) before entering the study. Written informed consent was obtained from all participants. Exclusion criteria were as follows: concurrent psychiatric disorders (DSM IV axis I, II cluster A or B); failure to respond to drug treatment in current depressive episode; previous resistance to antidepressant drugs, including SSRI; suicide risk score ≥3 on the HDRS; participation in other drug trials within the previous month; presence of delusions or hallucinations; history of substance abuse (including alcohol) in the past three months; pregnancy or lactation; serious organic illnesses in the past 6 months; frequent or severe allergic reactions; concomitant use of other psychotropic drugs (benzodiazepines were allowed) and blockers or catecholamine-depleting agents; current structured psychotherapy.

Study variables. Demographic and clinical data were collected. Likewise, any other relevant clinical information to the study was recorded: number of previous episodes, age at first depressive episode, melancholic features and medical history.

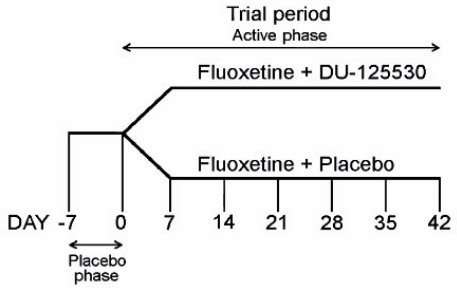

Figure 1
Clinical study design. Patients entered in a single-blind placebo phase of 3–7 days. Patients showing a reduction of 25% or greater of their HDRS score or with a decrease to below 18 at day 0 were excluded. Patients entering the study were randomized on day 0 to one of two treatment arms: fluoxetine + placebo or fluoxetine + DU-125530.

The primary variable of the clinical trial was the HDRS score. Sustained response was defined as a 50% or greater decrease in the admission HDRS score maintained until day 42, allowing a 5% variation during intermediate visits. Sustained remission was defined as an HDRS score of 8 or less maintained until endpoint. Secondary variables were the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI). Safety was assessed by means of biochemical variables and vital signs. ECGs were performed at admission, 2 weeks after beginning active treatment and at the end of the study. Plasma concentration of fluoxetine was obtained at 3 weeks of treatment and at the end of the trial.

Study design. The design of the study (Figure 1) was the same as that of a previous study assessing the effect of pindolol addition to fluoxetine treatment (Perez *et al.*, 1997) and had two active treatment arms: fluoxetine + placebo and fluoxetine + DU-125530 after a placebo run-in phase.

Placebo phase. After obtaining informed consent, patients entered a single-blind placebo run-in period of 3–7 days. Patients showing a ≥25% reduction of their admission HDRS score or an HDRS score lower than 18 during this period were excluded.

Active phase. Patients entering the study were randomized and assigned (day 1) to one of two treatment arms: fluoxetine 20 mg·day^{-1} plus placebo or fluoxetine 20 mg·day^{-1} plus DU-125530 (20 mg·day^{-1}). Patients, investigators and all personal participating in the study were unaware of the treatments (double-blind). The active phase lasted for 6 weeks. Clinical assessments were carried out on day 1 and every 7 days (±3 days) until day 42. Compliance was assessed by direct questioning patients and by counting returned pills and capsules at follow-up visits. Side effects were requested at each visit.

The study was approved by the Ethics Committee of the Hospital de Sant Pau and was registered with the US National Institutes of Health Protocol Registration System (NCT01119430). An independent researcher (Ignasi Gich, MD, Department of Clinical Pharmacology, Hospital de Sant Pau), not involved in the clinical trial, carried out the randomization by means of computer-generated random numbers.

Data treatment and statistical analyses.

The planned sample size for this study was 100 randomly assigned patients (50 in each treatment group), chosen to provide approximately 75% power to detect a difference in the percentage of responders at endpoint of 60% for fluoxetine plus placebo an 80% for fluoxetine plus DU-125530 using a one-sided 0.05 level test. Given the absence of previous trials using DU-125530, the use of one-sided test was considered to be more appropriate than increasing the sample size. Thus, one-sided *P*-values were used in safety and efficacy analyses. Data are given as means (SD). All scores were computed using a last observation-carried-forward (LOCF) approach. All analyses were done by intention to treat. Additional analysis of the observed cases (OC) was carried out. An interim analysis was performed at $n = 50$ (half of the planned sample), which met the criteria to stop the trial.

Main analysis was performed using repeated-measures ANOVA, with time (eight time points) as the within-subjects factor and group (fluoxetine + placebo vs. fluoxetine + DU-125530) as the between-subjects factor. A Huynh–Feldt correction was used where the assumption of sphericity was violated (uncorrected d.f. reported). Further differences were assessed by means of *post hoc* analyses. All randomized patients who had a baseline and at least one post-baseline score were included in the analyses. One-way ANOVA (treatment group as the between-subjects factor) was used to examine group differences with other clinical variables. Additionally, a survival analysis was done to establish the velocity of each treatment arm. All statistics were performed by means of statistical package for Windows SPSS 17.0.

Results

Characterization of DU-125530 as a 5-HT$_{1A}$ receptor antagonist: preclinical studies

Quantitative receptor autoradiography. The binding of the 5-HT$_{1A}$ receptor agonist [^{3}H]8-OH-DPAT and the corresponding antagonist [^{3}H]WAY-100635 to rat brain structures was inhibited by DU-125530 at low nanomolar concentrations, as illustrated in Figure 2A. Displacement curves of DU-125530 against the two radioligands, as generated from microdensitometric data, fitted to the one site binding competition model (Figure 3). The calculated pIC$_{50}$ values of DU-125530 for both ligands did not differ among the regions examined (Table 2).

In the human hippocampus (Figure 2B), DU-125530 also displaced [^{3}H]WAY-100635 binding with high affinity and produced monophasic displacement curves (not shown). The pIC$_{50}$ values calculated for the CA1 hippocampal field and the perirhinal cortex are reported in Table 3.

Electrophysiological studies. We examined the ability of DU-125530 to reverse the inhibition of the discharge rate of DR 5-hydroxytryptaminergic neurones induced by the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT and the SSRI fluoxetine. The administration of DU-125530 (67–134 μg·kg^{-1} i.v.) did not alter the firing rate of 5-hydroxytryptaminergic neurones by itself (1.9 ± 0.3 spikes per second vs. 1.7 ± 0.3 spikes per second in baseline conditions; n.s.; $n = 7$). However, DU-125530 fully reversed the decrease in firing rate induced by 8-OH-DPAT (1.2–4.8 μg·kg^{-1} i.v.) in all neurones examined ($F_{3,12} = 3.9$; $P < 0.04$; $n = 5$; Figure 4A,C). The subsequent administration of increasing doses of WAY-100635 (5–60 μg·kg^{-1} i.v.) did not increase the 5-hydroxytryptaminergic firing rate further, indicating full antagonism by DU-125530.

Similarly, DU-125530 (67–134 μg·kg^{-1} i.v.) reversed the reduction in DR 5-hydroxytryptaminergic firing rate produced by fluoxetine (0.8–4 mg·kg^{-1} i.v.) ($F_{3,15} = 4.0$; $P < 0.03$; $n = 6$; Figure 4B,D). Likewise, the subsequent administration of WAY-100635 (5–20 μg·kg^{-1} i.v.) did not augment the reversal elicited by DU-122530.

DU-12530 also reversed the effect produced by 8-OH-DPAT on medial prefrontal cortex pyramidal neurones in the few cases examined (see two examples in Figure 4E,F).

Microdialysis studies. We assessed the putative antagonist properties of DU-125530 at pre- and post-synaptic 5-HT$_{1A}$ receptors controlling 5-HT release *in vivo* in rats and mice (WT and 5-HT$_{1A}$ receptor *knockout*-KO) using four different experimental models: (i) antagonism of systemic 8-OH-DPAT-induced reduction of 5-HT release; (ii) reversal of paroxetine-induced reduction of 5-HT release (with local 5-HT reuptake inhibition in medial prefrontal cortex; mPFC); (iii) reversal of local 8-OH-DPAT application in mPFC; and (iv) augmentation of SSRI effect on extracellular 5-HT in mPFC.

Rat experiments. The systemic administration of DU-125530 (3 mg·kg^{-1} s.c.) did not significantly modify 5-HT release in mPFC (vehicle + vehicle, $n = 6$; vehicle + DU-125530, $n = 7$). However, its administration (3 mg·kg^{-1} s.c.) prevented the reduction of 5-HT release evoked by 50 μg·kg^{-1} s.c. 8-OH-DPAT (treatment $F_{1,7} = 7.8$, $P < 0.03$; time $F_{15,105} = 2.4$, $P < 0.01$ and treatment × time interaction $F_{15,105} = 5.3$; $P < 0.0001$; Figure 5A). To test the capacity of DU-125530 to antagonize the actions of 5-HT at somatodendritic 5-HT$_{1A}$ autoreceptors, we used an experimental paradigm in which an SSRI (e.g. paroxetine) is administered systemically while locally blocking the 5-HT transporter (SERT) with citalopram in the sampling forebrain area. In these experimental conditions, the systemically administered SSRI cannot further block SERT in the sampling area (e.g. mPFC), but it does in midbrain, where the increase in extracellular 5-HT activates 5-HT$_{1A}$ autoreceptors, thus reducing terminal 5-HT release (Romero and Artigas, 1997). In these conditions, paroxetine (3 mg·kg^{-1} s.c.) significantly reduced 5-HT release in mPFC, an effect significantly antagonized by DU-125530 administration (3 mg·kg^{-1} s.c.) (time $F_{15,120} = 38.7$; $P < 0.0001$ and treatment × time interaction $F_{15,120} = 3.5$; $P < 0.0001$; Figure 5B).

To examine the ability of DU-125530 to block post-synaptic 5-HT$_{1A}$ receptors, we locally applied 8-OH-DPAT in

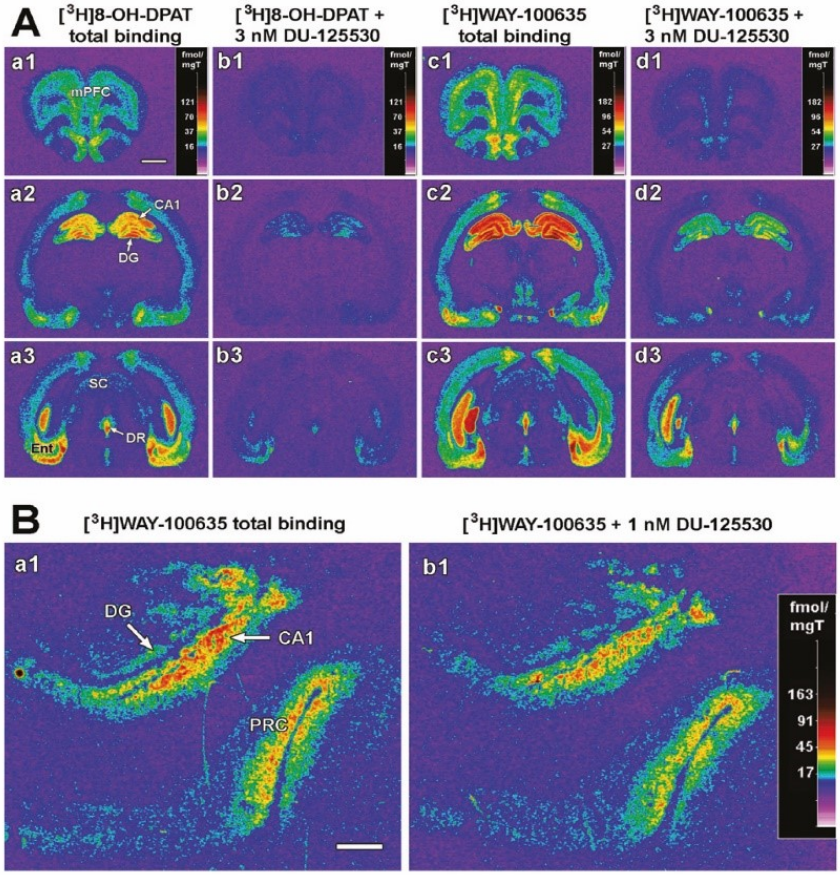

Figure 2

(A) Pseudocolour images from autoradiograms obtained from rat brain sections at different brain levels (prefrontal cortex, hippocampus and midbrain-upper pons) incubated with 0.5 nM [^{3}H]8-OH-DPAT alone (a1–a3) and in the presence of 3×10^{-9} M DU1255530 (b1–b3), or incubated with 0.5 nM [^{3}H]WAY-100635 alone (c1–c3) and in the presence of 3×10^{-9} M DU1255530 (d1–d3). Note that DU-1255530 inhibits [^{3}H]8-OH-DPAT and [^{3}H]WAY-100635 binding in all structures, including CA1, DG (dentate gyrus), DR (dorsal raphe), Ent (entorhinal cortex), mPFC (medial prefrontal cortex) and SC (superior colliculus). Bar = 2 mm. (B) Pseudocolour images from autoradiograms obtained from human hippocampal sections incubated with 0.5 nM [^{3}H]WAY-100635 alone (a1) or in the presence of 10^{-9} M DU-1255530 (b1). CA1, CA1 hippocampal field; DG, dentate gyrus; PRC, perirhinal cortex. Bar = 2 mm.

the mPFC by inverse microdialysis. The extensive occupancy of 5-HT$_{1A}$ receptors in mPFC by local 8-OH-DPAT inhibits excitatory inputs to the dorsal raphe (DR), thereby reducing 5-HT neuronal activity and terminal 5-HT release (Celada *et al.*, 2001). The local application of 100 μM 8-OH-DPAT in mPFC markedly reduced local extracellular 5-HT concentration. Subsequent systemic administration of DU-125530 (3 mg·kg^{-1} s.c.) significantly attenuated this reduction (time $F_{15,135} = 14.5$; $P < 0.001$ and treatment × time interaction $F_{15,135} = 2.7$; $P < 0.002$; Figure 5C) [note that saline rapidly increased extracellular 5-HT due to the injection stress (Adell *et al.*, 1997), yet the effect disappeared rapidly].

Finally, DU-125530 augmented the increase of extracellular 5-HT in mPFC evoked by (i) 3 mg·kg^{-1} paroxetine (time $F_{15,270} = 6.7$; $P < 0.0001$; treatment × time interaction $F_{15,270} = 2.3$; $P < 0.005$; Figure 5D); and (ii) 10 mg·kg^{-1} s.c. fluoxetine (time $F_{15,300} = 41.9$; $P < 0.0001$; treatment × time interaction $F_{15,300} = 1.8$; $P < 0.04$; fluoxetine + vehicle, $n = 9$; fluoxetine + DU-125530, $n = 13$; data not shown).

Mouse experiments. The systemic administration of DU-125530 (3 mg·kg^{-1} s.c.) alone had no effect on the extracellular 5-HT concentration in mPFC of wild-type mice (WT) (vehicle + vehicle, $n = 5$; vehicle + DU-125530, $n = 5$) nor in 5-HT$_{1A}$ receptor knock-out mice (KO) (vehicle + vehicle, $n = 5$; vehicle + DU-125530, $n = 4$). However, DU-125530 prevented the reduction of 5-HT release induced by 0.5 mg·kg^{-1} s.c. 8-OH-DPAT in WT mice (treatment $F_{1,10} = 16.4$; $P < 0.005$; time $F_{15,150} = 4.1$; $P < 0.0001$; treatment × time interaction $F_{15,150} = 2.7$; $P < 0.005$; Figure 6A).

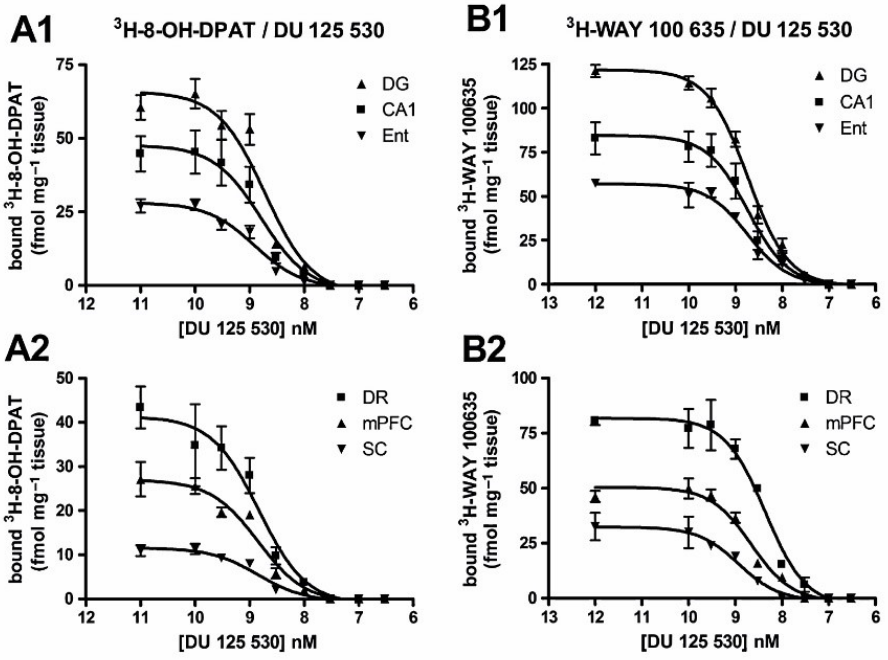

Figure 3

Displacement of [^{3}H]8-OH-DPAT (A1,A2) and [^{3}H]WAY-100635 (B1,B2) binding by DU1255530 in the hippocampus (CA1), DG, DR (Ent), mFPC and SC of the rat. Data points are means ± SEM of three animals and were obtained by microdensitometric analysis of autoradiograms.

Table 2

Relative binding affinities (pIC_{50}) of DU-125530 for [^{3}H]8-OH-DPAT and [^{3}H]WAY-100635 binding sites in various regions of the rat brain

Area	[^{3}H]8-OH-DPAT pIC_{50} ± SD	[^{3}H]WAY-100635 pIC_{50} ± SD
CA1	8.8 ± 0.1	8.7 ± 0.1
DG	8.7 ± 0.1	8.7 ± 0.1
Ent	8.9 ± 0.1	8.7 ± 0.1
DR	8.8 ± 0.2	8.4 ± 0.1
mPFC	8.9 ± 0.1	8.7 ± 0.1
SC	8.9 ± 0.1	8.9 ± 0.2

CA1, Ammon's horn area 1 of hippocampus; DG, dentate gyrus; DR, dorsal raphe nucleus; Ent, entorhinal cortex; mPFC, medial prefrontal cortex; SC, superior colliculus.

Table 3

Relative binding affinities (pIC_{50}) of DU-125530 for [^{3}H]WAY-100635 binding sites the CA1 hippocampal field and the perirhinal cortex of two human control cases

Area	[^{3}H]WAY-100635 pIC_{50} ± SD
CA1 case A	8.6 ± 0.1
CA1 case B	8.7 ± 0.2
PRC case A	8.8 ± 0.1
PRC case B	8.4 ± 0.1

CA1, Ammon's horn area 1; PRC, perirhinal cortex.

As expected, 0.5 mg·kg^{-1} s.c. 8-OH-DPAT did not reduce 5-HT release in the mPFC of 5-HT_{1A} receptor KO mice, and the change in 5-HT concentration produced by vehicle + 8-OH-DPAT was identical to that produced by DU-125530 + 8-OH-DPAT (Figure 6B) [a moderate, fast increase in extracellular 5-HT was produced, as a result of handling and injection stress (Adell *et al.*, 1997)].

The systemic administration of fluoxetine (20 mg·kg^{-1} s.c.) increased extracellular mPFC 5-HT concentration significantly more in KO mice than in WT mice (genotype effect $F_{1,8} = 6.0$; $P < 0.05$; time effect $F_{15,120} = 14.7$; $P < 0.0001$; time × genotype interaction $F_{15,120} = 2.5$; $P < 0.005$; Figure 6C). The subsequent administration of DU-125530 (3 mg·kg^{-1} s.c.) significantly enhanced extracellular 5-HT concentration in WT mice, up to the level seen in 5-HT_{1A} receptor KO mice after fluoxetine administration (time $F_{15,135} = 20.3$; $P < 0.0001$; genotype × time interaction $F_{15,135} = 2.6$; $P < 0.002$; Figure 6D).

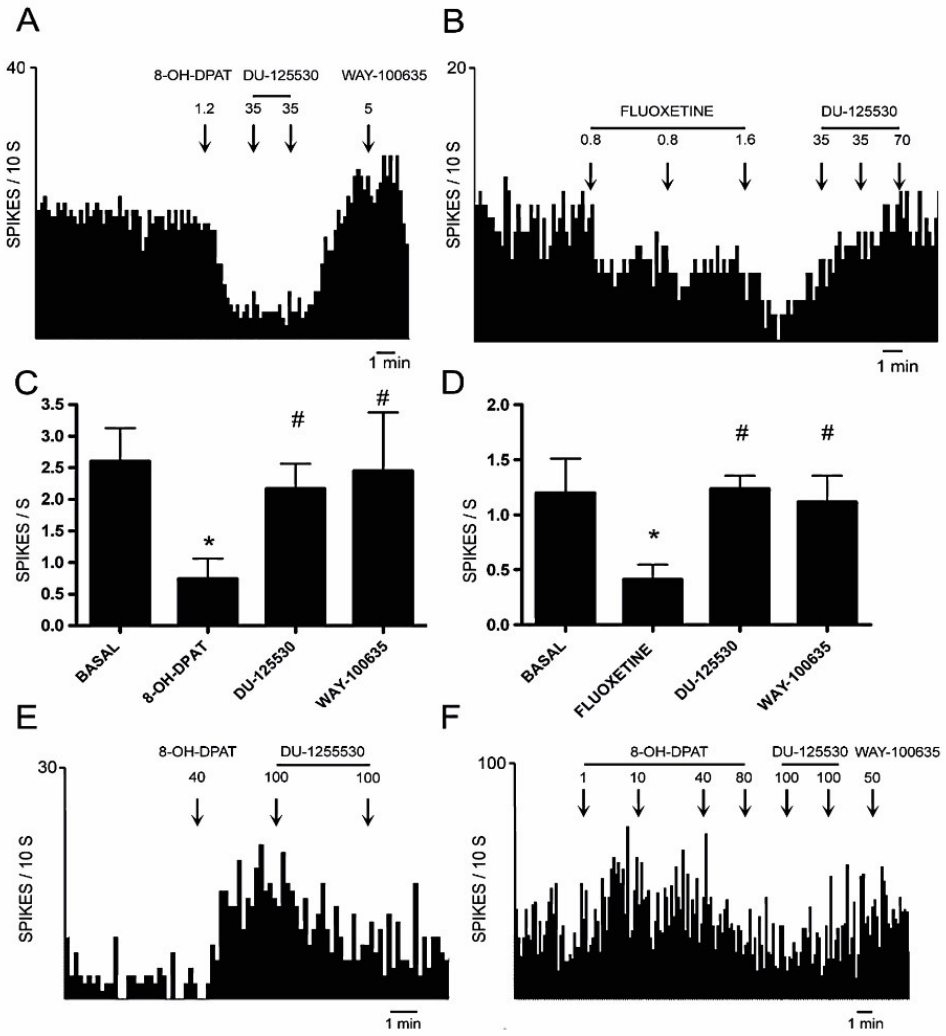

Figure 4

(A,B) Representative integrated firing rate histograms of two 5-hydroxytryptaminergic neurones showing the inhibition of discharge rate induced by the i.v. administration of 8-OH-DPAT (A) and fluoxetine (B) as well as the reversal of the effect by the subsequent administration of DU-125530 in both cases. Note that the administration of the prototypical 5-HT$_{1A}$ receptor antagonist WAY-100635 after DU-125530 did not evoke any further effect on firing rate indicating a complete reversal of the action of 8-OH-DPAT by DU-125530. (C,D) Bar graphs showing the inhibitory effect on 5-HT cell firing produced by 8-OH-DPAT (C) or fluoxetine (D) and the reversal of these effects by DU-125530. (E,F) Integrated firing rate histograms of two pyramidal cells in mPFC, which were identified by antidromic stimulation from the DR. The administration of the 5-HT$_{1A}$ agonist 8-OH-DPAT evokes excitations (E) or excitations at low doses followed by inhibitions at higher doses (F). Both effects are reversed by the subsequent administration of DU-125530, showing its antagonist properties at post-synaptic 5-HT$_{1A}$ heteroreceptors. Arrows mark the time of drug administration.

Clinical characterization of DU-125530 in accelerating/enhancing fluoxetine antidepressant response

Fifty-seven patients were screened and entered the study between May 2004 and November 2007. Seven patients were excluded before randomization due to placebo response. Therefore, 50 patients with major depression diagnosis (MDD) finally entered the active phase (Figure 7). Twenty-five were randomly assigned to fluoxetine plus DU-125530 arm and 25 to fluoxetine plus placebo arm (Figure 1). No differences were found in demographic or clinical variables between the two groups (Table 4).

Neither the percentage of patients with first depressive episode (51% receiving DU-125530, 48% receiving placebo) nor the percentage of melancholic features (23% and 14%.

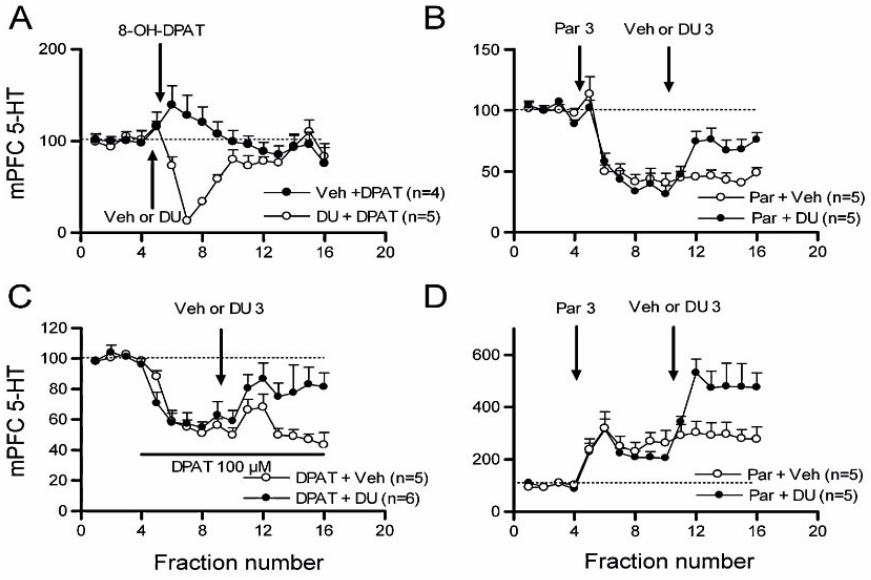

Figure 5

In vivo microdialysis experiments showing the antagonism/reversal exerted by DU-125530 in the different experimental models used in rats. The extracellular 5-HT concentration (shown as percentages of baseline; set to 100, dotted line) in mPFC was used in all instances. (A) Prevention by DU-125530 of the 8-OH-DPAT-induced reduction of 5-HT release. (B) Reversal by systemic administration of DU-125530 of the paroxetine (Par)-induced decrease in 5-HT release in mPFC during the local perfusion of citalopram by reverse dialysis. (C) Reversal by systemic DU-125530 administration of the effects produced by local application of 8-OH-DPAT on mPFC. (D) Augmentation by DU-125530 of the paroxetine-induced increase in mPFC extracellular 5-HT levels. Arrows mark systemic injections. Doses are given in mg·kg^{-1}. Horizontal bars indicate local perfusion by inverse microdialysis. See text for statistical analysis.

respectively) differed between groups. Current episode duration ranged from 1 to 6 months for 63.6% of patients receiving fluoxetine + DU-125530 and for 54.5% of those receiving fluoxetine + placebo. Treatments were generally well tolerated with no differences in the incidence of adverse events between the two groups (32% for DU-125530, 16% for placebo, $\chi^2 = 1.75$; $P = 0.16$). Regarding sexual dysfunction, one patient treated with DU-125530 reported anorgasmia. Five patients were withdrawn from the clinical trial because of side effects and two due to patient's decision. Repeated-measures ANOVA for blood pressure did not show a significant main effect of time × group ($F_{7,196} = 0.5$, $P = 0.8$) nor a group effect ($F_{1,27} = 1.3$, $P = 0.3$). Heart rate showed a similar non-significant time × group effect ($F_{7,182} = 1.1$, $P = 0.4$) and no group effect ($F_{1,26} = 0.1$, $P = 0.8$). These results indicated that vital signs were stable during the study and with no significant differences between groups. Plasma concentration of fluoxetine at days 14 and 42 did not differ between groups. At day 14, fluoxetine mean values were 57.5 ng·mL^{-1} (SD = 31.7) in the fluoxetine + DU-125530 group and 66.4 ng·mL^{-1} (SD = 31.9) in the fluoxetine + placebo group ($t = -0.9$, $P = 0.4$). At day 42, fluoxetine values were 86.1 ng mL^{-1} (SD = 46.3) in the fluoxetine + DU-125530 group and 119 ng·mL^{-1} (SD = 76.3) in the fluoxetine + placebo group ($t = -1.7$, $P = 0.1$).

Regarding the main analysis with HDRS scores, repeated-measures ANOVA showed a significant effect of time ($F_{7,280} = 96.6$; $P < 0.001$) but not of the group ($P = 0.9$) nor of time × group interaction ($P = 0.6$). Figure 8A shows the temporal evolution of cumulative percentages of sustained responses for both groups. A tendency towards higher sustained responses in the fluoxetine + DU-125530 group was seen at 3–4 weeks, but it did not reach statistical significance.

The response rate of patients receiving DU-125530 + fluoxetine was similar to that of patients receiving fluoxetine + placebo. The survival analysis (Figure 8B) confirmed the absence of significant differences between the two treatment arms, being mean survival times until first response 44 days for DU-125530 and 37 days for placebo (log-rank, $\chi^2 = 0.3$, $P = 0.6$).

We performed an additional analysis with the OC ($n = 21$ for DU-125530; and $n = 20$ for placebo), which gave essentially the same results (group effect: $F_{1,39} = 0.1$, $P = 0.8$; time × group effect: $F_{7,273} = 0.5$, $P = 0.8$).

Discussion and conclusions

The present study shows that DU-125530 is a high-affinity and silent 5-HT$_{1A}$ receptor antagonist in rodent brain that prevents and reverses the actions of 5-HT and 5-HT$_{1A}$ receptor agonists (8-OH-DPAT) at pre- and post-synaptic 5-HT$_{1A}$ receptors. It binds to rat and human 5-HT$_{1A}$ receptors with low nM affinity, and it antagonizes the actions of the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT and SSRIs (fluoxetine and paroxetine) in

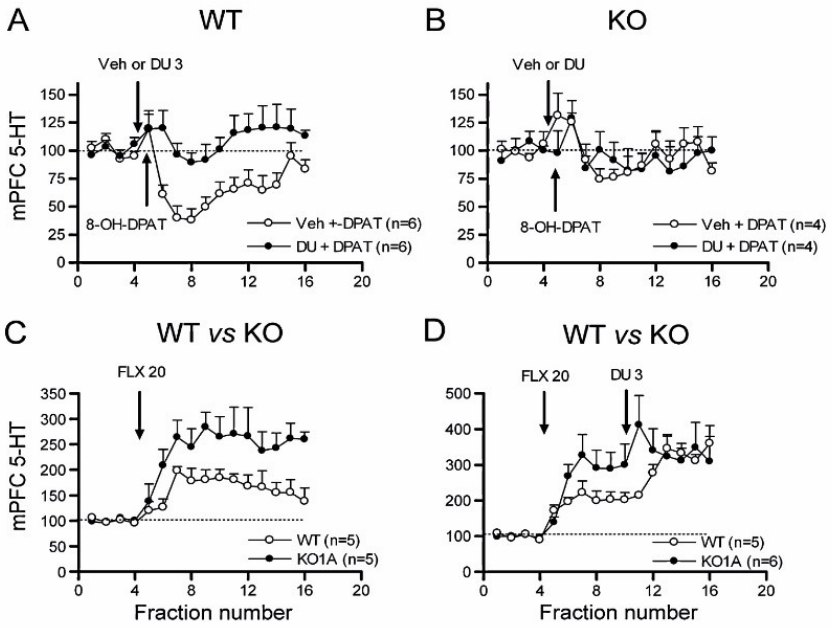

Figure 6

In vivo microdialysis experiments in wild type (WT) and 5-HT$_{1A}$ receptor knock out (KO1A) mice showing the effects of DU-125530. The extracellular 5-HT concentration (shown as percentages of baseline; set to 100, dotted line) in mPFC was used in all instances. (A) Prevention by DU-125530 of the reduction in 5-HT output induced by systemic 8-OH-DPAT administration in WT mice. (B) Lack of effects of systemic administration of 8-OH-DPAT and DU-125530 in KO mice. (C) Comparison of the effects of systemic injections of fluoxetine (FLX) in WT versus KO mice. (D) Augmentation of the effects of fluoxetine by DU-125530 in WT mice but not in KO mice. Note that the treatment of WT with fluoxetine + DU-125530 increases extracellular 5-HT concentration to the same extent than fluoxetine alone in KO mice. Arrows mark systemic injections. Doses are given in mg·kg^{-1}. See text for statistical analysis.

electrophysiological and microdialysis experimental paradigms. As a consequence, DU-125530 augments the elevation in forebrain extracellular 5-HT concentration produced by SSRIs by preventing the 5-HT$_{1A}$ autoreceptor-mediated negative feedback evoked by these agents (Artigas *et al.*, 1996). Despite these excellent pharmacological properties, DU-125530 did not accelerate nor enhance the antidepressant action of fluoxetine. To our knowledge, this is the first study testing the 5-HT$_{1A}$ receptor augmentation hypothesis (Artigas, 1993; Artigas *et al.*, 1996) with a selective 5-HT$_{1A}$ receptor antagonist and consequently will affect antidepressant drug design.

Preclinical studies

Overall, the preclinical data support that DU-125530 interacts with 5-HT$_{1A}$ autoreceptors and post-synaptic 5-HT$_{1A}$ receptors in a manner similar to that of the prototypical antagonist WAY-100635 (Forster *et al.*, 1995; Fletcher *et al.*, 1996), which – unlike DU-125530 – is not available for human use. Indeed, DU-125530 displaced the agonist (^{3}H-8-OH-DPAT) and antagonist (^{3}H-WAY-100635) binding to rat and human 5-HT$_{1A}$ receptors with nM affinity and blocked the effects of exogenous (8-OH-DPAT) and endogenous (5-HT) 5-HT$_{1A}$ receptor agonists on (i) 5-HT neurone activity and (ii) 5-HT release, in rats and mice, as previously observed with WAY-100635 using the same experimental paradigms (Romero and Artigas, 1997; Casanovas *et al.*, 1999; Celada *et al.*, 2001; Romero *et al.*, 2003; Lladó-Pelfort *et al.*, 2011). Moreover, DU-125530 augmented the increase in extracellular 5-HT induced by SSRI to an extent comparable with that produced by WAY-100635 (Romero and Artigas, 1997; Hervas *et al.*, 1998). Interestingly, the dose used in the present preclinical experiments appears to fully occupy 5-HT$_{1A}$ receptors, as (i) no further antagonism was produced by WAY-100635 when it was used after DU-125530, and (ii) the 5-HT increase induced by fluoxetine + DU-125530 on extracellular 5-HT in WT mice was identical to that produced by fluoxetine alone in 5-HT$_{1A}$R KO mice.

The ability of DU-125530 to antagonize post-synaptic 5-HT$_{1A}$ receptors is shown by the following: (i) pilot electrophysiological experiments [reversal of 8-OH-DPAT-induced effects on mPFC pyramidal neurones, an effect depending on post-synaptic 5-HT$_{1A}$ receptor activation (Lladó-Pelfort *et al.*, 2011)]; and (ii) microdialysis experiments in which the systemic administration of DU-125530 significantly reversed the reduction in 5-HT release evoked by the activation of mPFC 5-HT$_{1A}$ receptors by local 8-OH-DPAT administration, as previously observed with WAY-100635 (Celada *et al.*, 2001). Indeed, the direct activation of pyramidal 5-HT$_{1A}$ receptors in mPFC neurones attenuates the excitatory input onto DR 5-HT

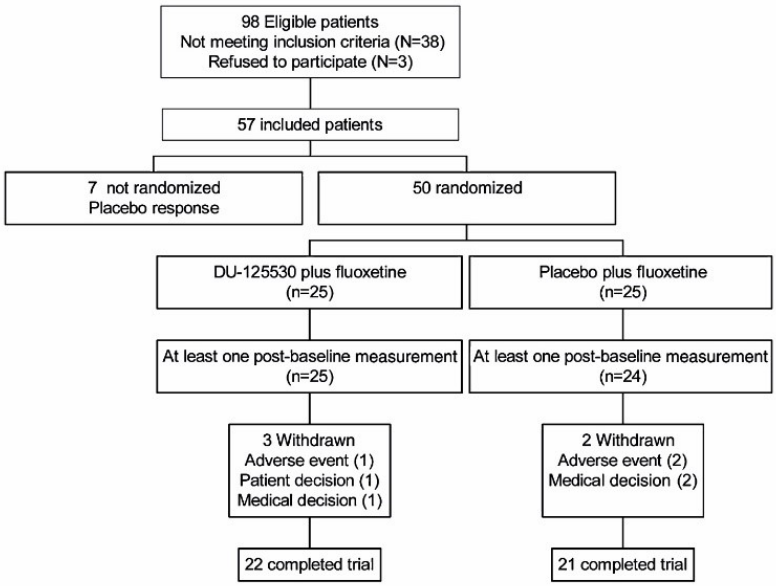

Figure 7

Flow diagram of subject progress through the phases of a randomized trial.

Table 4

Demographic and clinical variables of the two treatment groups

Variables	DU-125530 (n = 25)	Placebo (n = 25)	χ^2/t	P
Gender (% females)	83.3	84	0	n.s.
Age	42.1 (11.5)	42.5 (13.9)	0.9	n.s.
Family psychiatric history (% present)	64	36	3.7	n.s.
No previous depressive episode (%)	41.7	54.2	0.1	n.s.
Age at first depressive episode	34 (14.3)	38.2 (15.5)	0.9	n.s.
Number of depressive episodes (including current episode)	2.6 (2.8)	1.7 (1.1)	1.4	n.s.
Concomitant treatment (% patients taking)			2.4	n.s.
No treatment	25	35.7		
Benzodiazepines	56.2	28.6		
Hypnotic	12.5	21.4		
Benzodiazepines plus hypnotic	6.2	14.3		
HDRS				
Pre	24.7 (3.7)	25.6 (4.4)	0.7	n.s.
Post	13 (9.6)	11.1 (6.8)	0.7	n.s.
MADRS				
Pre	31.3 (4.5)	32.6 (5.1)	0.9	n.s.
Post	14.8 (12)	14 (10.3)	0.2	n.s.
CGI				
Pre	4.7 (0.6)	4.7 (0.6)	0.3	n.s.
Post	2.5 (1.3)	2 (1)	1	n.s.

DU-125530 = patients treated with fluoxetine + DU-125530; Placebo = patients treated with fluoxetine + placebo. Dta are shown as means (with SD). n.s., non-significant; pre, pretreatment; post, post treatment.

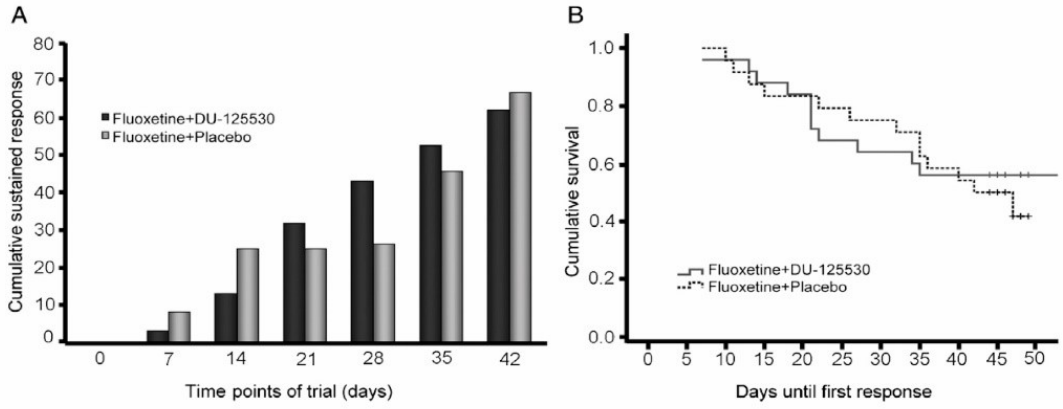

Figure 8

(A) Bar graph showing the cumulative percentages of patients with sustained response throughout the trial period. Repeated-measures ANOVA showed a significant effect of the treatment but not of the group or treatment × group interaction. (B) Kaplan–Meier survival analyses of days until response.

neurones (Celada *et al.*, 2001) and evokes a subsequent reduction of forebrain 5-HT release. The data show that the systemic administration of DU-125530 antagonized this effect, showing a clear antagonist action at post-synaptic 5-HT$_{1A}$ receptors.

Despite its *in vitro* affinity for α_1-adrenoceptors (~10 times lower than for 5-HT$_{1A}$ receptors), DU-125530 did not reduce 5-HT release by itself, as expected from blockade of raphe α_1-adrenoceptors (Vandermaelen and Aghajanian, 1983; Bortolozzi and Artigas, 2003). Moreover, no cardiovascular side effects were observed in patients treated with fluoxetine + DU-125530. Both observations allow us to discount a significant occupancy of α_1-adrenoceptors at the doses used. Likewise, DU-125530 shows nM affinity for dopamine D_2 receptors (Table 1). However, none of the observed preclinical effects of the compound can be attributed to interaction with such D_2 receptors. Likewise, no side effects derived from D_2 receptor blockade (e.g. extrapyramidal symptoms) were observed in patients treated with fluoxetine + DU-125530.

Thus, the present preclinical results indicate that:

- DU-125530 displays equal nM affinity at pre- and post-synaptic 5-HT$_{1A}$ receptors.
- DU-125530 is a silent pre- and post-synaptic 5-HT$_{1A}$ receptor antagonist in rodent brain.
- DU-125530 cancels the 5-HT$_{1A}$ receptor-mediated negative feedback induced by SSRIs, thereby augmenting their increase of extracellular 5-HT concentration.

Clinical trial

The present clinical trial was conducted to examine whether the augmentation of 5-hydroxytryptaminergic function that resulted from the blockade of 5-HT$_{1A}$ autoreceptors was translated into an increased speed or efficacy of the antidepressant fluoxetine. To this end, the trial design was identical to that used previously to examine the augmenting action of pindolol (Perez *et al.*, 1997). Due to the lack of selective 5-HT$_{1A}$ receptor antagonists available for clinical use, pindolol was used in past studies testing the 5-HT$_{1A}$ receptor augmentation strategy (Artigas, 1993; Artigas *et al.*, 1994; 1996; Perez *et al.*, 1997; Bordet *et al.*, 1998; Zanardi *et al.*, 1998; Ballesteros and Callado, 2004; Portella *et al.*, 2011). However, the addition of DU-125530 to fluoxetine treatment did not enhance nor accelerate its antidepressant action in a population of depressive patients with clinical characteristics similar to those included in previous studies (Perez *et al.*, 1997; 1999). This difference cannot be attributed to pharmacokinetic factors as fluoxetine plasma levels were similar to those previously reported in the fluoxetine + pindolol study (Perez *et al.*, 2001) and did not differ between treatment arms.

However, several remarkable differences exist between pindolol and DU-125530. PET scan studies have revealed a preferential occupancy of pre-synaptic versus post-synaptic 5-HT$_{1A}$ receptors by pindolol, using ^{11}C-WAY-100635 as a ligand (Artigas *et al.*, 2001; Martinez *et al.*, 2001). However, DU-125530 shows a comparable occupancy of pre- and post-synaptic 5-HT$_{1A}$ receptors using the same ligand (Rabiner *et al.*, 2002). Thus, the occupancy of pre- and post-synaptic 5-HT$_{1A}$ receptors by the dose of DU-125530 used herein (20 mg·day^{-1}) is 50–60% in most individuals tested (Rabiner *et al.*, 2002). In contrast, the pindolol dose used in most clinical studies (7.5 mg·day^{-1}) (Martinez *et al.*, 2001) produced an occupancy of 40% pre-synaptic and 18% post-synaptic 5-HT$_{1A}$ receptors. These PET scan studies are paralleled by electrophysiological (Romero *et al.*, 1996) and histological (Castro *et al.*, 2000; Serrats *et al.*, 2004) studies showing a preferential affinity of pindolol for pre- versus post-synaptic 5-HT$_{1A}$ receptors. Hence, pindolol antagonized the 5-HT$_{1A}$ autoreceptor-mediated inhibition of 5-hydroxytryptaminergic cell firing produced by SSRIs (Romero *et al.*, 1996), but not the activation of hippocampal 5-HT$_{1A}$ receptors induced by 5-HT and 5-HT$_{1A}$ receptor agonists (Romero *et al.*, 1996; Tada *et al.*, 1999). In agreement, G-protein activation studies indicated a significantly higher potency of pindolol for 5-HT$_{1A}$ autoreceptors than for post-

synaptic 5-HT_{1A} receptors in the hippocampus and entorhinal cortex in rat, guinea pig and human brain (Serrats *et al.*, 2004). Likewise, pindolol showed a greater affinity for pre- than for post-synaptic 5-HT_{1A} receptors in human brain (Castro *et al.*, 2000). A second difference between pindolol and DU-125530 lies in the partial agonist character of pindolol (Newman-Tancredi *et al.*, 1998). Pindolol may increase cortical catecholamine release via activation of mPFC 5-HT_{1A} receptors when administered alone (see Artigas *et al.*, 2001). However, it appears unlikely that this property can be relevant in a pharmacological situation dominated by the excess 5-HT – and therefore high 5-HT_{1A} receptor activation – produced by SSRIs.

The inability of DU-125530 to accelerate or augment the antidepressant action of fluoxetine is likely to be attributable to its simultaneous blockade of pre- and post-synaptic 5-HT_{1A} receptors, given the enhanced post-synaptic 5-HT_{1A} receptor activation produced by several antidepressant drug classes in rodents (Haddjeri *et al.*, 1998; Blier and Ward, 2003). The present data support that this process may also occur in human brain. Thus, while 5-HT_{1A} autoreceptor blockade augments pre-synaptic 5-HT function by preventing the negative feedback at pre-synaptic (raphe) level, the simultaneous blockade of post-synaptic 5-HT_{1A} receptors in corticolimbic areas may cancel this effect. Moreover, the present results indicate that other 5-HT receptors (e.g. 5-HT_4) (Lucas, 2009) are involved in the antidepressant action of fluoxetine, because the extensive blockade of post-synaptic 5-HT_{1A} receptors did not cancel the clinical effect of fluoxetine, as it would be expected if post-synaptic 5-HT_{1A} receptors were the only mediators of its antidepressant action.

Limitations of the study

The wide range of techniques and methodologies used in preclinical studies to characterize the action of DU-125530 in rodent brain support a full antagonist action of this agent at pre- and post-synaptic receptors with a low level of uncertainty. In any case, we carried out a reduced number of experiments to examine the action of DU-125530 at post-synaptic 5-HT_{1A} receptors using electrophysiology. However, microdialysis data are fully supportive of such an antagonist action of post-synaptic 5-HT_{1A} receptors. In the clinical trial, the main limitation of the study is that only one dose of DU-125530 was used, based on PET scan data (Rabiner *et al.*, 2002). Given the antidepressant properties of post-synaptic 5-HT_{1A} receptor activation in animal models (see above), it is unknown whether a lower DU-125530 dose, leading to a less post-synaptic 5-HT_{1A} receptor occupancy would have augmented the antidepressant effects of fluoxetine. Trial design does not appear to be a limitation, as we used the same one than in a previous trial (Perez *et al.*, 1997), which was able to detect significant differences between two similar arms (fluoxetine + placebo vs. fluoxetine + pindolol).

In summary, the present study shows that DU-125530 is an excellent antagonist of pre- and post-synaptic 5-HT_{1A} receptors. Despite this, its addition to fluoxetine did not accelerate nor enhance its antidepressant properties in patients with major depression. These results show that simultaneous blockade of pre- and post-synaptic 5-HT_{1A} receptors does not improve the antidepressant actions of SSRI, indicating that post-synaptic 5-HT_{1A} receptor activation is required to achieve an enhancement of the antidepressant effects of SSRIs, a conclusion relevant to antidepressant drug design.

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Conflicts of interest

EA has received consulting and educational honoraria from several pharmaceutical companies including Eli Lilly, Sanofi-Aventis, Lundbeck and Pfizer, and he has participated as main local investigator in clinical trials from Eli Lilly, Bristol-Myers and Sanofi-Aventis and also as national coordinator of clinical trials from Servier and Lundbeck. VP has received educational honoraria from the following pharmaceutical companies: Sanofi-Aventis, Lundbeck, Pfizer and Eli Lilly. FA has received consulting or educational honoraria from Boehringer-Ingelheim, Eli Lilly, Lundbeck and Pierre Fabre. The rest of authors declare no conflicts of interest related directly or indirectly to this work.

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10.3 Treball 3

Títol: 5-HT1A receptor and antidepressant treatment. Review and meta-analysis of pindolol in nonresistant depression.

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Abstract:

Background and purpose: Serotoninergic system has been studied last 60 years when first antidepressants were discovered and it was observed that his action module the system. The aim of tis paper is briefly review the serotoninergic system and drugs that act on the serotoninergic 5-HT1A receptor: pindolol, antidepressants (vilazodone and vortioxetine), azapirones, and antipsychotics. Additionally a meta-analysis study of the efficacy of the pindolol is done focusing on capability to induce and antidepressant early response (week 2).

Method: *Meta-analysis*: Efficacy was assessed by the number of treatment responders at week 2. There were included randomized clinical trial which investigate the benefits of pindolol (doses range from 7.5 to 20 mg/day) plus antidepressant in patients with diagnosis of unipolar depressive disorder without history of treatment resistance. Efficacy was assessed by the number of patients that presented a fast response: decrease of >50% in depression rating scores 2 weeks after random allocation and beginning of the treatment.

Results: *Meta-analysis***:** Outcome favored pindolol at 2 weeks' time (relative risc [RR]=1.65; 95% CI= 1.11 to 2.43; *P*=0.016).

Conclusions: This review and meta-analysis represent further evidence of enhancement and acceleration efficacy of antidepressant treatment by pindolol. The role of 5-HT1A receptor is an important clue of antidepressant treatment.

Introduction

Major depression is a common disease with a calculated annual prevalence of 6.6% and life prevalence of 16.2% (Kessler et al., 2003, Kessler et al., 2005).Women are affected twice than men and the highest incidence is on early adulthood (Kessler et al., 2003, Haro et al., 2006). This fact implies an important economic and social impact considering that depressive patients have many or more days of work inability as other who suffer from chronic diseases as asthma or heart diseases (Wang et al., 2003). World Health Organization (WHO) calculated consequences of depression and it was found that it was the first cause of disability-adjusted life year in the occidental world as result of 98.7 million of people at every ages were affected (World Health Organization, 2008). Depression entails also impairment on global health of the patient because it worsen prognosis of comorbid illness (Evans et al., 2005, Gildengers et al., 2008) and also increases the mortality (Cuijpers and Schoevers, 2004).

Since antidepressant treatments beginning on 1950s, we have effective drugs for depressive disorder treatment. Over the years, antidepressant agents have been more selective on receptor acting so adverse effects have decreased and tolerability has increased.

Nevertheless, antidepressant treatments have important limitations. On one side, they need 2-3 weeks for starting their clinical effect and symptom remission takes 10-14 weeks (Trivedi et al., 2006). While treatment doesn't starting their clinical effect the patient continue suffering from negative consequences of the depressive illness: emotional distress (which increases suicidal risk) and impairment in different areas, and this fact reveals the need to accelerate the beginning of the antidepressant response. The other main limitation is the low effectiveness of antidepressant agents. Clinical trials reveals response rates of 60-70% and remission rats of 25-40% (Stahl, 2000, Thase et al., 2001, Undurraga and Baldessarini, 2012). In the STAR*D trial, which is more similar to usual clinical practice, results are worse than expected: response after the first antidepressant treatment is 55% and remission is only achieved by 27% of the patients (Trivedi et al., 2006).

Thus, it is compulsory and urgent to develop strategies for reducing latency of response of antidepressants and for increasing the effectiveness.

Serotoninergic system has been studied last 60 years when first antidepressants were discovered and it was observed that his action module the system. The aim of tis paper is briefly review the serotoninergic system and drugs that act on the serotoninergic 5-HT1A receptor: pindolol, antidepressants (vilazodone and vortioxetine), azapirones, and antipsychotics. Additionally a meta-analysis study of the efficacy of the pindolol is done focusing on capability to induce early antidepressant response.

The serotoninergic system:

Serotonin is an ancient neurotransmitter which exist since primitive stages of life on the Earth. It is probably that its existence goes back to more than 800 million years ago on the evolutionary scale (Hay-Schmidt, 2000). It is the widely distributed neurotransmitter in central nervous system (CNS) and is involved in a large number of physiological functions such as: hormone secretion, cardiovascular regulation, immune functions and thermoregulation. It is also implicated in a variety of behavioral functions including circadian rhythm awake-sleep, appetite, aggressive and sexual behavior, sensory-motor reactivity, pain and learning (Lucki, 1998).

The serotoninergic neurons are originated mainly in the brainstem dorsal and medial raphe nuclei, and their axons are highly bifurcated with high density of axonal varicosities which denotes they are ideally structured for influencing the functions of several regions of the CNS (Beaudet and Descarries, 1976). There are a relatively low number of serotoninergic neurons; it it is estimated that the human brain contains a 250,000 5-HT neurons of a total of 10^{11} in the CNS (Jacobs and Azmitia, 1992).

Some of serotoninergic projections form classical chemical synapses, but most contacts release 5-HT by paracrine stimulus. Serotonin neurons have a slow and steady activity and act as pacemaker neurons showing a strong homeostasis (Vandermaelen and Aghajanian, 1983). Once serotonin is released at the synaptic cleft and it binds to the presynaptic and postsynaptic receptors, is reuptaked thorugh the serotonine transporter (SERT) with the aim of recycling and optimize the neurotransmitter and also for ending the action. Part of non-reuptaked serotonin is degraded by the monoamine oxidase enzyme (MAO) (Olivier, 2015).

Under normal conditions, serotoninergic neurons activity is under control through several imputs from different CNS areas with other neurotransmitters involved and also through autoinhibitory mechanism wich implies the 5-HT1A presynaptic receptors activation (Artigas et al., 1996a). On one side, the serotoninergic system gets glutamatergic inputs from the forebrain areas (Fink et al., 1995, Celada et al., 2001, Martin-Ruiz et al., 2001a), inhibitory inputs from local GABAergic interneurons (Bagdy et al., 2000, Gervasoni et al., 2000, Varga et al., 2001), tonic noradrenergic aferences from the pontine nuclei (Vandermaelen and Aghajanian, 1983, Peyron et al., 1996, O'Leary et al., 2007), and dopaminergic aferences from the midbrain dopaminergic nuclei (Martin-Ruiz et al., 2001b).

The serotoninergic system has multiple serotonin receptors in both presynaptic and postsynaptic levels; these last ones act as heteroreceptors in diverse neuronal groups such as GABAergic and glutamatergic neurons (Adell et al., 2002, Artigas, 2012)

The fact that this system is composed by a little number of neurons, with a widespread distribution in CNS. It presents a broad axonal branching and high variety of receptors at presynaptic and postsynaptic levels, also like heteroreceptors. Is controlled through inputs from

different CNS areas and also presents tightly auto regulatory mechanisms. These anatomical and electrophysiological characteristics make the serotoninergic system a complex network and little changes in the activity of this reduced group of neurons may affect large areas of the brain.

The serotoninergic receptors (5-HTR).

Nowadays, 7 families of serotonin receptors (5-HT1R to 5-HT7R) are described, some of them with several subtypes and variations, which results in a total of 14 (Raymond et al., 2001). All of these receptors are protein G-coupled with the exception of the 5-HT3R gating a cation-permeable ion channel. Some of these receptors are molecularly different(Palacios, 2016). Protein G-coupled signal transmission is highly varied and it changes between cerebral areas and also it depends on the interactions with other receptors and regulators and several biological conditions (physiological, pathological and treatment)(Millan et al., 2008).

Our recommendation is consulting the reviews of Hoyer, Raymond and Artigas for additional information of serotoninergic receptors (Hoyer et al., 1994, Raymond et al., 2001, Artigas, 2013).

5-HT1 Receptors: This family has 5 members: 1A, 1B, 1C, 1D, 1E, 1F.They are mainly coupled through G proteins to the inhibition of adenylyl cyclase and to wide range of other intracellular signaling pathways.

5-HT1A Receptor:

It is the most studied serotoninèrgic receptor. It is very close to β2-adrenergic receptor and this fact explains the high affinity of some beta-blockers as pindolol, for this receptor (Guan et al., 1992, Zifa and Fillion, 1992).

Its main function is to inhibit adenyl cyclase and to open potassium channels(Hannon and Hoyer, 2008). Therefore, it has been described the inhibition of different enzymes, kinases channels and the stimulation or inhibition of other second messengers (Barnes and Sharp, 1999, Raymond et al., 2001).

On mammal brains, 5-HT1A receptors have been located on both presynaptic and postsynaptic level (Celada and Artigas, 1993, Sharp et al., 2007). They are located on presynaptic level on sertoninergic neurons of raphe nuclei, as autoreceptor, mainly at dorsal and medial raphe nuclei. On postsynaptic level, as heteroreceptor, it is mainly located in cortico-lymbic regions: hippocampus, septum and entorhinal cortex, at glutamatergic and GABAergic neurons (Santana et al., 2004, Sharp et al., 2007).

5-HT1A receptor plays a crucial role in the regulating mechanism of the serotoninergic system. On its presynaptic and somatodendritic location in raphe nuclei it takes part in self-regulation and self-inhibition system. The experimental trials have revealed that activation of presynaptic 5-HT1A receptor by endogenous serotonin provokes a cell hyperpolarization by opening potassium channels. This mechanism makes cellular electrical activity stop or decrease (Blier and de Montigny, 1987, Sprouse and Aghajanian, 1987), acting as negative feedback mechanism and leading to the inhibition of serotonin discharge (Araneda and Andrade, 1991, Ashby et al., 1994, Craven et al., 2001). 5HT1A receptor acts as a serotonin neuron activity modulator, it prevents excess of stimulation and contributes to maintain the slow and regular discharge rate

(pacemaker activity) of this system (Celada et al., 2004). It is like a safety valve in case of excessive excitatory input, such as those provoked by stress that would produce and increase of serotonin in the extracellular space (Artigas, 2013).

Most of antidepressant agents (MAOIs, SSRI, tricyclic antidepressants, SNRIs), produce an increasing of extracellular serotonin, by blocking reuptake or metabolism. This increase is detected especially on the raphe, where the highest concentration of serotonin neurons and reuptake transporter is located (Bel and Artigas, 1992, Invernizzi et al., 1992). Antidepressants produce an extracellular non physiological increase of serotonin and this fact becomes in the activation of autoregulation mechanism mediated by 5-HT1A receptor (Artigas, 1993). Thus, antidepressant agents interfere with the homeostasis of serotoninergic system and to compensate it neuron self-adaptive mechanisms were activated and serotoninergic transmission to the forebrain is diminished(Artigas et al., 2006). Continued administration of SSRIs (antidepressant chronic treatment) desensitizes 5-HT1A receptors of raphe neurons which decreases negative feedback system and allows the serotonin augmentation in the synaptic cleft (Blier and de Montigny, 1994, Hervas et al., 2001, El Mansari et al., 2005), leading to antidepressant clinical effect. Similar feed-back mechanism is suggested by the evidence from primates and human neuroimaging trials with positron emission tomography (PET) (Nord et al., 2013).

Another self-regulation mechanism of serotoninergic neurons is the 5-HT1B receptor, also with presynaptic location (axon terminal) and with inhibition function (Sari, 2004).

Postsynaptic location of 5-HT1A receptor is widely in limbic structures and it has been implicated in pathophysiology of depression and response to antidepressants (Celada et al., 2004, Savitz et al., 2009). Several preclinical trials have revealed that activation of 5-HT1A postsynaptic receptors is a necessary step to achieve antidepressant function for monoaminergic drugs (Haddjeri et al., 1998, Blier and Ward, 2003, Scorza et al., 2012).

The 5-HT1A receptor has been studied by PET techniques and postmortem trials. **Neuroimaging trials** have detected a binding potential (BP) decline of this receptor in different cortical brain areas (Drevets et al., 1999, Drevets et al., 2000, Sargent et al., 2000, 2004, Meltzer et al., 2004, Drevets et al., 2007, Hirvonen et al., 2008, Moses-Kolko et al., 2008). However, the results aren't homogeneous and there are some trials that detected increase of the receptor binding potential. Three studies of the same group find increases of BP in cortical brain areas in depressed patients not recently exposed to antidepressant compared to depressed medicated patients or controls (Parsey et al., 2006a, Parsey et al., 2010, Hesselgrave and Parsey, 2013). One study only detect increase of BP in depressed men, being the raphe the main affected region (Kaufman et al., 2015) and a last study show increased BP in depressed patients with major lethality suicide attempt (Sullivan et al., 2015). Regarding the relation between antidepressant

response and BP of 5-HT1A receptor, the majority of trials didn't detected changes on it (Bhagwagar et al., 2004, Moses-Kolko et al., 2007, Miller et al., 2009, Lanzenberger et al., 2013) but two trials did it (Lothe et al., 2012, Hesselgrave and Parsey, 2013). To sum up, PET data seem to show a dysregulation of the 5-HT1A receptor in frontal, temporal and limbic cortex with a decline of the receptor expression in patients with depressive disorder which is not related to antidepressant treatment.

In **post mortem** studies, reduction of 5-HT1A receptor expression have been detected on samples of patients with depression who died by suicide in several cortical regions (Cheetham et al., 1990, Lopez et al., 1998, Lopez-Figueroa et al., 2004, Anisman et al., 2008, Szewczyk et al., 2009). Nevertheless, opposite results have been noticed in other trials (Matsubara et al., 1991, Arango et al., 1995, Underwood et al., 2012) and other trials didn't find differences (Arranz et al., 1994, Lowther et al., 1997a, Stockmeier et al., 1997). In addition, investigation in patients with depression and mortality cause different to suicide revealed decrease in cortical expression of 5-HT1A receptor (Bowen et al., 1989, Stockmeier et al., 2009). Differences in brain stem, mainly at raphe, have been noticed also with increased expression of 5-HT1A receptor in dorsal raphe nuclei (DRN) (Stockmeier et al., 1998) and the rostral aspects of the DRN (Boldrini et al., 2008) and other trials detect decline of the receptor on caudal aspects of the DRN (Arango et al., 2001, Boldrini et al., 2008).

The interpretation of results from neuroimaging and postmortem trials is difficult because there are many influences: pharmacological treatment, alcohol consumption and previous suicide attempt (Savitz et al., 2009), PET technic and measure of results, radio ligand used in neuroimaging and pot-mortem time may affect the results (Stockmeier, 2003).

Genetic polymorphism of 5-HT1A receptor: A single nucleotide polymorphism (SNP) has been described in the promoter region of the codifying gen (5-HT1AR rs6295 (-1019C/G)) and it is related with increase of the receptor expression (Lemonde et al., 2003). G/G genotype has been found associated with an increased expression of 5-HT1A receptors in the raphe (David et al., 2005, Parsey et al., 2006b) and this fact could be responsible of the reduction of the firing rate in this neurons and the decline of the serotoninergic transmission from this area. These genetic variations are higher in depressive patients (Neff et al., 2009, Kishi et al., 2013), depressive patients with suicide attempt and patients with depression related to interferon treatment (Lemonde et al., 2003, Parsey et al., 2006b, Kraus et al., 2007). This association is not detected in every trials (Serretti et al., 2007, Wasserman et al., 2007, Videtic et al., 2009, Gonzalez-Castro et al., 2013) and neither with response to antidepressant treatment (Zhao et al., 2012a).

It seems the function of 5-HT1A receptor is different depending on presynaptic or postsynaptic location. Considering presynaptic level (raphe) is related to self-regulation mechanisms and up-

regulation process increases risk of depression and suicide. At postsynaptic level, the results are too discrepant to obtain a conclusion.

Self-regulation mechanism of serotoninergic system by 5-HT1A receptor is probably involved in latency response of serotoninergic antidepressant drugs. This is the origin of the strategy proposed by professor Artigas (Artigas, 1993), based on using total or partial antagonist agents to this receptor with the finality of desensitization, decreasing negative feedback and improving latency period and achieve and augmented response to SSRI. On 90's, this investigator used the unique drug approved for human use and with these properties**: pindolol** (Artigas et al., 1994). Pindolol is a drug with special properties because is an adrenergic beta-blocker with high affinity for 5-HT1A and 5-HT1B receptors (the last one only in mice), so antagonizes physiological effects mediated by this receptor as hypothermia or hormonal secretion in both humans and mice (Middlemiss and Tricklebank, 1992, Raurich et al., 1999). The hypothesis in treatment depression was that pindolol would desensitize 5-HT1A receptor and it would enhance serotoninergic transmission and clinical effect of SSRI by blocking auto-regulatory feed-back mechanism. The model was tested in animal models and experimental trials show that pindolol increases serotonin in forebrain and enhances serotoninergic transmission (Bel and Artigas, 1993, Artigas et al., 1996b, Dreshfield et al., 1996, Romero and Artigas, 1997).

On basis of this hypothesis a firs open clinical trial was done, using pindolol like antidepressant enhancer in depressive patients; the results were encouraging (Artigas et al., 1994). Afterwards, a double blind trial was done (pindolol versus placebo) using pindolol in combination with fluoxetine. In this trial, latency response decreased and global response to antidepressant treatment increased in the pindolol group (Perez et al., 1997).

Several clinical trials have been done after these mentioned with a total of 21 clinical trials comparing pindolol and placebo (see table 1). Two matters have been tested: 1) pindolol capability for accelerating antidepressant action and 2) pindolol capability for improving antidepressant global response.

On one hand, pindolol has positive effect on **accelerating** antidepressant response. Nine of 12 trials detect reduction of latency period response (Perez et al., 1997, Tome et al., 1997, Zanardi et al., 1997b, Bordet et al., 1998, Zanardi et al., 1998, Shiah et al., 2000, Isaac et al., 2003, Geretsegger et al., 2008, Portella et al., 2011). On the other hand, capability to **augmenting** antidepressant response offers more heterogeneous results and it depends on patient clinical characteristics. 1) Samples with patients affected by resistant depression show clear negative results (Moreno et al., 1997, Perez et al., 1999, Perry et al., 2004). There's only one trial with positive results in this case but with a small sample (9 patients) (Sokolski et al., 2004). 2) A total of 17 studies have been conducted in patients with major depression some of them include resistant patients in the sample. Of them, there are 10 trials that show positive result

(improvement of antidepressant response with pindolol) (Maes et al., 1996, Perez et al., 1997, Zanardi et al., 1997a, Maes et al., 1999, Smeraldi et al., 1999, Shiah et al., 2000, Zanardi et al., 2001, Isaac et al., 2003, Portella et al., 2011). One study detected increased response to pindolol only in patients with first depressive episode (Geretsegger et al., 2008). Furthermore, 7 trials don't find differences between pindolol and placebo (Berman et al., 1997, Tome et al., 1997, Bordet et al., 1998, Zanardi et al., 1998, Berman et al., 1999, Whale et al., 2010, Martiny et al., 2012).

Usual doses of pindolol was 7.5 mg/day. Neuroimaging studies done in humans have revealed that this dose leaded to low receptor occupancy and this is could be the reason of negative results in some clinical trials (Rabiner et al., 2000a). Three studies with higher doses of pindolol were performed: 2 of them show that pindolol shortened antidepressant response(Bordet et al., 1998, Portella et al., 2011) and one with negative results (Berman et al., 1999).

As new studies were published, three meta-analysis about the strategy of antidepressant treatment augmentation with pindolol have been performed (Ballesteros and Callado, 2004, Whale et al., 2010, Portella et al., 2011). All of them conclude that antidepressant-pindolol combination is better than using only antidepressant treatment, mainly in patient who aren't resistant to treatment.

5-HT1A receptor: other drugs

There are two new antidepressant drugs that present affinity to 5-HT1A receptor: vilazodone and vortioxetine.

Vilazodona is a strong serotonin reuptake inhibitor (Bartoszyk et al., 1997) and it also has high affinity for 5-HT1A receptor acting as partial antagonist (Bartoszyk et al., 1997, Page et al., 2002). Microdialysis trials reveal higher levels of extracellular serotonin in hippocampus and frontal cortex when vilazodone is administrated than using fluoxetine (Page et al., 2002) without chances on noradrenaline or dopamine levels (Hughes et al., 2005). Other experimental trials didn't find differences in serotonin levels when SSRIs vas combined with an agonist agent of 5-HT1A receptor, however it did when an antagonist agent of 5-HT1A receptor or vilazodone were dispensed (Hughes et al., 2005). Partial agonism of 5-HT1A receptor (acting as antagonist functionally) desensitizes it and allows faster increase of serotoninergic transmission leading to the activation of 5-HT1A postsynaptic receptors, fact that seems necessary to obtain an antidepressant response (Blier et al., 1997, Blier and Ward, 2003). Vilazodone has antidepressant effect on animal models, considering less effective higher dosage (Page et al., 2002) and in a neuroimaging study on humans was revealed 5-HT1A receptor occupancy with more affinity for presynaptic location (Rabiner et al., 2000b)

Clinical data in major depression: there are three clinical trial which compare effectiveness between vilazodone and placebo in major depression; a total of 1396 patients were included

(Rickels et al., 2009, Khan et al., 2011, Croft et al., 2014). Positive result was obtained in all of them. One detected improvement of symptoms at first week of treatment (Rickels et al., 2009) and other at second week (Croft et al., 2014). Nevertheless, one trial didn't found differences in remission of symptomatology at the end of the study (Khan et al., 2011). There's only one trial that includes comparison with an active antidepressant agent and vilazodone obtained better response than placebo but without differences in sustained response (Mathews et al., 2015).

Vortioxetine has a serotonin reuptake inhibitor function and also different range of affinity for several serotoninergic receptors (Sanchez et al., 2015). This fact modulates his antidepressant response and makes it different from other SSRIs. In fact, acute dispense of vortioxetina revealed higher increase of serotonin levels than only with SSRIs (Pehrson et al., 2013).

Vortioxetine has inhibitory function of serotonin reuptake and it occupies the transporter in a range from 50 to 80% at clinical doses (5 to 20 mg/day)(Sanchez et al., 2015). This occupancy is less than one it is necessary for achieving clinical response with SSRIs that is 80% (Meyer et al., 2004). It also is partial agonist of 5-HT1A receptor (Sanchez et al., 2015) so desensitize the receptor and interfere the inhibition mechanisms of serotoninergic neuron. Therefore has affinity for 5-HT1B receptor which is also implicated in self-inhibition mechanisms.

It also antagonizes 5-HT3 receptor and this could be responsible of augmentation of cortical serotonin that is associated with vortioxetina. Increase of serotonin at ventral hippocampus and medial prefrontal cortex (mPFC) is higher with the combination of a SSRI and 5-HT3 antagonist than with an isolated SSRI (Mork et al., 2012, Riga et al., 2016).

Vortioxetine is also a 5-HT1D presynaptic antagonist and this activity has demonstrated an augmentation of extracellular serotonin association with an SSRI (Pullar et al., 2004), which could be explained also by the 5-HT7 antagonist action (Bonaventure et al., 2007).

It hasn't got action on noradrenaline or dopamine reuptake process but it regulates the neurotransmission of this two by serotonin modulation. The increase of noradrenaline transmission at mPFC and ventral hippocampus is supposed to be related to 5-HT3 antagonism (Betry et al., 2015) and with 5-HT1A partial agonism (Suzuki et al., 1995, Suwabe et al., 2000).

It is also proposed the augmentation of dopamine mediated by vortioxetine but related with 5-Ht1A postsynaptic interaction mechanism (Rasmusson et al., 1994, Diaz-Mataix et al., 2005). Vortioxetine has dopamine extracellular effects only when 5-HT1A receptor is filled which strengthen the role of this receptor. Nevertheless, vilazodone doesn't produces this increase on noradrenaline and dopamine so other mechanisms different from 5-Ht1A are probably involved.

Vortioxetine increases acetylcholine and histamine at mPFC (Mork et al., 2012), also by interaction to serotoninergic receptors because it has low affinity by acetylcholine and histamine ones (Bang-Andersen et al., 2011). This has been related with positive effects on cognition.

To sum up, the effect of vortioxetine would be the result of its inhibitory action on SERT, interaction with other serotonin receptors involved in self-regulatory mechanisms in serotoninergic neurons and regulation of other neurotransmission systems. However, it is unknown the specific role of each receptor on the final effect of the drug (Betry et al., 2015).

Clinical data in major depression: Different trial for testing vortioxetina efficacy on major depression have been done: 14 placebo-controlled clinical trials (Alvarez et al., 2012, Baldwin et al., 2012b, Henigsberg et al., 2012, Katona et al., 2012, Jain et al., 2013, Mahableshwarkar et al., 2013, Boulenger et al., 2014, McIntyre et al., 2014, Jacobsen et al., 2015b, Mahableshwarkar et al., 2015a, Mahableshwarkar et al., 2015b, Mahableshwarkar et al., 2015c, Wang et al., 2015). Nine of these studies revealed positive results to the antidepressant. Positive result were observed also in a trial with patients whom didn't respond to firs antidepressant treatment (Montgomery et al., 2014). One study showed better efficacy on relapse prevention tan placebo (Boulenger et al., 2012). Other five open label trials were done for testing tolerability and long term efficacy (Baldwin et al., 2012a, Alam et al., 2014, Jacobsen et al., 2015a). There are also three meta-analyses that include placebo-controlled trials and all of them conclude on superiority of vortioxetine (Meeker et al., 2015, Pae et al., 2015, Thase et al., 2016).

On the other hand, vortioxetina improves cognition deficits associated to major depression (Katona et al., 2012, McIntyre et al., 2014, Mahableshwarkar et al., 2015c) and this effect seems to be related to its particular receptor profile more than with the antidepressant effect (Sanchez et al., 2015, McIntyre et al., 2016).

Antipsychotics with 5-HT1A receptor action: From long time ago antipsychotics have been used for major depressive disorder and there is positive evidence for several for them. Antidepressant effect is complex. Atypical antipsychotics have lower affinity for D2 receptor antagonism than typical ones but they interact with several serotoninergic receptors, mainly like antagonist of 5-HT2A receptor and also with high affinity for 5-HT2C R. Some antipsychotics have activity on 5-HT1A receptor too (Shelton and Papakostas, 2008) acting as antagonists and this fact could contribute with the increase of cortical dopamine (Masana et al., 2012). The modulation of serotoninèrgic receptors would produce rise of noradrenaline, dopamine and serotonin release on prefrontal cortex and accumbens nucleus which is related with improvement of depressive symptoms (Meltzer, 1991, Blier and Szabo, 2005).

There are different atypical antipsychotics that show affinity for 5-HT1A receptor. Aripiprazole, brexiprazole and ziprasidone are those whom most affinity present. Clozapine and olanzapine have low affinity for 5-Ht1A receptor "in vitro" but they act like agonist "in vivo" trials (Diaz-Mataix et al., 2005, Masana et al., 2012). Other are quetiapine, risperidone (Masana et al., 2012), cariprazine (Kiss et al., 2010), iloperidone (Kalkman et al., 2003) and lurasidone (Ishibashi et al., 2010).

Aripiprazole is one of most studied antipsychotic like enhancer antidepressant treatment, even on elderly population, with positive results in almost every trial (Berman et al., 2007, Marcus et al., 2008, Berman et al., 2009, Fava et al., 2012, Kamijima et al., 2013, Lenze et al., 2015).

Brexipiprazole is a partial agonist of 5-HT1A and D2 receptors and also acts like antagonist of 5-HT2A receptor (Eaves and Rey, 2016). Its action on 5-HT1A receptor is more powerful than aripiprazole. There are three clinical trials randomized and placebo-controlled which show its efficacy like adjuvant treatment with several antidepressants in patients with an inadequate response to treatment (Thase et al., 2015a, Thase et al., 2015b) and NCT00797966 study .

Cariprazine is a new antipsychotic drug that acts like D2 and D3 receptor partial agonist, with preference for D3 ones. It is also a weak partial agonist of 5-HT1A receptor and antagonist of 5-HT2B receptor with high affinity. Furthermore, it has low affinity for 5-HT2A, 5-Ht2C, alfa-1 and histamine receptors (Kiss et al., 2010). It is proposed for schizophrenia and bipolar disorder treatment and one clinical trial studied its role like adjuvant treatment in resistant depression with positive results (Durgam et al., 2016).

Quetiapine has been also widely tested in depression, both in monotherapy (https://clinicaltrials.gov/ct2/show/NCT01725282, Cutler et al., 2009, Weisler et al., 2009, Bortnick et al., 2011, Locklear et al., 2013) and combined with antidepressant agents (McIntyre et al., 2007, Chaput et al., 2008, Bauer et al., 2009, El-Khalili et al., 2010, Wijkstra et al., 2010), with positive results in most of the trials.

Two clinical trials placebo-controlled have tested **ziprasidone** for major depression**:** one as monotherapy treatment compared with placebo, which reveal negative results (Papakostas et al., 2012). But the second one, with ziprasidone as adjunctive therapy to escitalopram, resulted in favour of the antipsychotic (Papakostas et al., 2015).

There are two randomized, placebo-controlled studies that test **lurasidone** in treatment of unipolar depression and were done in depressive patients who had mixed episodes or any hypomanic symptom. It was compared with placebo and showed positive outcome for lurasidone (https://clinicaltrials.gov/ct2/show/NCT01421134, Suppes et al., 2016).

Azapirones: There are a family of drugs with agonist action on 5-Ht1A receptor. The group is composed by the next molecules: buspirone, gepirone, ipsapirone and zalopsirone. The affinity for 5-HT1A receptor changes depending on its location. They are total agonist at presynaptic level (on the raphe) and partial agonist at postsynaptic level (cortical-hippocampus) (Sprouse and Aghajanian, 1988). It is important knowing the differences between presynaptic and postsynaptic function of the 5-HT1A receptor for an accurate reading of the results. By one side, agonism of 5-HT1A receptor implies a decrease of the rate of release of serotoninergic neurons in the raphe with a decrease of total cortical serotonin. On the other side, it is necessary complete stimulation of 5-HT1A postsynaptic receptor for achieving antidepressant effect and

azapirones are partial agonist (Haddjeri et al., 1998). So, in acute therapy with azapirones, endogenous serotonin will be replaced and activation of 1A receptor will decrease which is opposite to antidepressant effect. In animal models, azapirones dosages are very high and have positive results like antidepressant treatment, but in humans occupancy of receptors seem to be lower (Rabiner et al., 2000b). It is proposed that higher dose is related with more activation of 5-HT1A postsynaptic receptor and this is the reason of positive results in preclinical trials but doubtful in clinical ones (Artigas, 2013).

Azapirones have demonstrated efficacy on generalized anxiety disorder, better than placebo and equal to antidepressant and psychotherapy but worse than benzodiazepines (Chessick et al., 2006) and they have bad tolerability because of digestive side effects

Like antidepressants its use is controversial despite of there are studies with positive results in comparison with placebo (Kishi et al., 2014) because of their usual side effects (gastrointestinal discomfort, dizziness, insomnia, tachycardia and paresthesia) and treatment dropout because of lacking efficacy. Finally, trials testing efficacy of azapirone as adjunctive treatment didn't find differences with placebo (Kishi et al., 2014).

Meta-analysis:

Methods:

Data from a previous meta-analysis done by our investigation group (Portella et al., 2011) has been updated in the current one. We included randomized clinical trial which investigate the benefits of pindolol (doses range from 7.5 to 20 mg/day) plus SSRIs in patients with diagnosis of unipolar depressive disorder without history of treatment resistance. Efficacy was assessed by the number of patients that presented a fast response: decrease of >50% in depression rating scores 2 weeks after random allocation and beginning of the treatment. The Hamilton Depression Rating Scale (HDRS) was selected as outcome measure and the relative risk (RR) for clinical response was chosen as the effect size to extract and combine by using a random effect model. The I^2 index was used to estimate the heterogeneity between trials. Additionally, the number-needed-to treat (NNT) was estimated by taking the inverse of the pooled risk difference. The meta-analysis was performed with Stata v10 (StataCorp 2007, College Station, TX)

Results:

To update the previous meta-analysis we included the results of a new study published after that one was performed, reported by Martiny (Martiny et al., 2012), it included data response at day 19, so we updated the meta-analysis of early response (at 2 weeks) with the results of this new trial.

The analysis was performed by random effects model and it was estimated the RR for early clinical response, updated with the results of the new study. The results favored the efficacy of the augmentation with pindolol (RR=1.65; 95% CI= 1.11 to 2.43; p=0.016). The same results were obtained in cumulative meta-analysis. Figure 1. (forest plot +graphic cumulative meta-analysis). Pindolol augmentation offered 17% more efficacy (RD=0.17; 95% CI= 0.05 to 0.28) and the NNT for obtaining a clinical response was 6 (95% CI=4 to 20).

Between-study heterogenity was calculated by Q test which was significant but also by I^2 index that resulted in 47%, which represents moderate heterogeneity. According to the sensitivity analysis, no single trial exerted a significant influence on the pooled estimate. By deleting 1 trial at the time, the pooled RR ranged from 37.5% to 51.7%. Several asymmetry test were done for detection of publication bias or small effect bias and they all were no significant.

Discussion:

Data from preclinical, neuroimaging, post-mortem trials and clinical trials with molecules which interact with 5-HT1A receptor show the different function between presynaptic (raphe) and postsynaptic (cortical) location. The activity on presynaptic level seems related to latency period of antidepressant response. The desensitization by using drugs like pindolol or other 5-HT1A partial agonists/antagonists could be useful for reducing time to clinical response of antidepressant therapy. On the other side, postsynaptic level is related with the global antidepressant response. No differences were detected between depressed patients who were treated with fluoxetine and one 5-HT1A antagonist and those who received placebo, so it is proposed that 5-Ht1A receptor must be activated for achieving and improvement in antidepressant response (Scorza et al., 2012). Therefore, in way to optimize antidepressant treatment it would be necessary an opposite effect between both 5-Ht1A receptor locations. Firstly, activity of 5-HT1A presynaptic receptors should be decreased and postsynaptic ones increased. Studies with small-interfering RNS (siRNA) confirm his hypothesis. The siRNA are pieces of RNA administered with SSRIs as vehicle. SSRI conduct de siRNA to the raphe, where is the highest 5-HT reuptake concentration (Cortes et al., 1988). On the raphe siRNA blocks 5-HT1A receptor expression selectively on serotoninergic neurons and antidepressant effect is obtained in animal models of depression (Bortolozzi et al., 2012b, Ferres-Coy et al., 2012).

The meta-analysis results sustain the pindolol's efficacy for accelerating antidepressant response in those patients without resistance to antidepressant treatment. Nonetheless, there is controversy about variability observed in those trials and the contributing factors. On one side, it is proposed that this effect could be related to an agonist interaction on the 5-HT1A receptor, not with an antagonist one, because of the discrepancy in the results of preclinical a laboratory trials. Information from total studies done show despite of pindolol has agonist activity "in vitro"

(Newman-Tancredi et al., 1998), it acts like partial antagonist in mice and rat brains (Artigas et al., 2001). On the other side, some authors have impute pindolol effect to its action on postsynaptic 5-HT1A receptors. But human neuroimatge studies done with WAY-100635 showed that pindolol presents mainly occupancy of raphe 5-HT1A receptor (Martinez et al., 2000, Rabiner et al., 2000a, Martinez et al., 2001), which means affinity was greater for presynaptic receptors than postsynaptic receptors. Pindolol effect must be owed to the desensitization of 5-HT1A receptor on presynaptic location and the modulation of self-inhibition mechanisms of serotoninergic neurons.

Novel antidepressant agents (vortioxetine and vilazodone) with affinity for 5-HT1A receptor have shown clinical efficacy but not improvement in latency of response and they haven't demonstrate superiority over other antidepressants (Sahli et al., 2016, Thase et al., 2016). Azapirones have demonstrated only modest efficacy as antidepressant treatment (Kishi et al., 2014) and antipsychotics with antidepressant effect it is not completely related to their activity on the 5-HT1A receptor because they act to other receptors. Therefore, it seems pindolol's capability for accelerating the antidepressant response could be related with its particular pharmacological profile: its greater affinity for presynaptic receptors with antagonist activity and the limited interference on the postsynaptic transmission which allows endogenous serotonin function and the antidepressant effect(Celada et al., 2013). This hypothesis is supported by data coming from vilazodone trials on animals where it is observed greater efficacy with lower doses than with higher doses. Higher doses could compete with endogenous serotonin and result in a less postsynaptic 5-HT1A receptor activation (Page et al., 2002) and this effect could cancel the beneficious effect of presynaptic 5-HT1A receptor desensitization.

Considering depression implies high social and health impact, it is compulsory investigation on new strategies for improving antidepressant response, global prognosis and evolution of this disorder.

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Study	Aim	Antidepressant and pindolol doses (mg/day)	Patients	Main variable response	Length	Efficacy at the end of study	Onset response
Maes et al., 1996	augmentation	trazodone 100+PIN 7.5 vs trazodone 100 + PBO vs trazodone 100+ fluoxetina 20	33 inpatient, 3 patients ATD free, the other were ATD resistant	HDRS≤50%	4 weeks	PIN>PBO	NE
Perez et al., 1997	acceleration	fluoxetina 20 mg+ PIN 7.5 vs PBO	111 outpatient ATD free	HDRS, days to response and sustained response	6 weeks	PIN>PBO	PIN>PBO
Berman et al 1997	Acceleration	Fluoxetina 20 mg+PIN 10 or 7.5 vs PBO	43 outpatient	HDRS≤50% or HDRS <10	6 weeks	PIN=PBO	PIN=PBO
Tome et al., 1997	acceleration	paroxetine 20 + PIN 7.5 vs PBO	80 outpatient ATD free	MADRS ≤ 50%	6 weeks	PIN=PBO	PIN>PBO *
Zanardi et al., 1997	acceleration	Paroxetine 20+ PIN 7.5 x 1 week. Paroxetine 20+PBO x 4 weeks. paroxetine 20+ PIN 7.5 x 4 weeks (three arms of treatment)	63 patient ATD free	HDRS< 8	1-4 weeks	PIN>PBO, PINx4 weeks> PINx1 week	PIN>PBO
Moreno et al., 1997	augmentation	Fluoxetina, bupropion, desipramine +PIN 7.5 vs PBO	10 patient with resistant depression	HDRS <10 o HDRS ≤50%	2 weeks	PIN=PBO	NE
GlaxoSmithKline 1997 Study. Published in Whale 2010	acceleration	Paroxetine 20+PIN 7.5 vs PBO	164 patients with non-psychotic depression outpatients	MADRS	6 weeks	PIN=PBO	PIN=PBO
Zanardi et al., 1998	acceleration	fluvoxamine 300 +PIN 7.5 vs PBO	72 patients ATD free	HDRS ≤ 8	6 weeks	PIN=PBO	PIN>PBO
Bordet et al., 1998	acceleration	paroxetine 20 + PIN 15 vs PBO	100 patients ATD free	HDRS ≤ 10	4 weeks	PIN=PBO	PIN>PBO
Berman et al., 1999	acceleration	fluoxetina 20+PIN 7.5 o 10 vs PBO	86 outpatients ATD free, almost all with chronic and recurrent depression	HDRS ≤50% or HDRS <10	6 weeks	PIN=PBO	PIN=PBO
Smeraldi et al., 1999	augmentation	Sleep deprivation + PIN 7.5 vs PBO	40 inpatients with bipolar depression	HDRS ≤ 8	9 weeks	PIN>PBO	NE
Maes et al., 1999	augmentation	fluoxetina 20 + PIN 7.5 vs fluoxetina 20 vs fluoxetina 20 + mianserina30 (three arms of treatment)	31 inpatients with resistant and non-resistant depression	HDRS ≤50%	5 weeks	PIN>PBO	NE

Perez et al., 1999	augmentation	clomipramine 150, fluoxetina 40, fluvoxamine 200, paroxetine 40 + PIN 7.5 vs PBO	80 outpatient with resistant depression	HDRS ≤ 8 o HDRS <50%	10 weeks	PIN=PBO	NE
Shiah et al., 2000	acceleration	ECT (6 sessions) + PIN 7.5 vs PBO	20 patients with resistant depression and patient ATD free	HDRS (29) <12	2 weeks	PIN>PBO	PIN>PBO
Zanardi et al 2001 (Zanardi et al., 2001)	augmentar	Fluvoxamina 300+PIN 7.5 vs PBO	155 inpatient with major depression or bipolar depression (delusion/not delusion)	HDRS ≤ 8	6 weeks	PIN>PBO	NE
Isaac et al., 2003	acceleration	minalcipram 100 + PIN 7.5 vs PBO	78 inpatient and outpatient ATD free	Change in MADRS	6 weeks	PIN>PBO	PIN>PBO
Perry et al., 2004	augmentation	ISRS(fluoxetina, paroxetine o sertraline) + PIN 7.5 vs PBO in a hemi-crossover design	42 outpatient with resistant depression	HDRS ≤50% and HDRS <15	6 weeks	PIN=PBO	NE
Sokolski et al., 2004	augmentation	paroxetine 40 + PIN 7.5 (single dose) vs PBO	9 patient with resistant depression	Change in HDRS	4 weeks	PIN>PBO	NE
Geretsegger et al., 2008	augmentation	paroxetine 20 +PIN 7.5 vs PBO	50 inpatients with unipolar and bipolar depression	HDRS (17) ≤50% HDRS ≤ 8. Sustained response	4 weeks	PIN>PBO#	PIN>PBO ##
Portella et al, 2011	acceleration	Citalopram 20 (First 3 days ev and after po) + PIN 15 vs PBO	30 patient antidepressant free	HDRS ≤50% sustained until endpoint or HDRS≤8 until endpoint	6 weeks	PIN>PBO	PIN>PBO
Martiny et al 2012	augmentation	Venlafaxine 150 + PIN 20 (single dose) vs PBO	31 patient with depression	HDRS (17) ≤50% HDRS (17) ≤ 8.	19 days	PIN=PBO	NE

Table 1. Double blind randomized studies with pindolol vs placebo for treatment of depression (unipolar and bipolar). PIN=pindolol. PBO=placebo. NE: not evaluated. Antidepressant doses in mg/day. Total doses of pindolol is shown, in mg/day, usually in three time/day if other information is not indicated.

***** in one of the centers of the study, in the other center: PIN=PBO.

Only in patient never treated with antidepressant and patients with bipolar depression. ## Only shortened response in patients with bipolar depression.

Abbreviations: HDRS: Hamilton depression rating scale (usually 21), ≤ 50%: decreases more or 50% in the rating scale. Montgomery-Asberg Depression Rating Scale (MADRS)

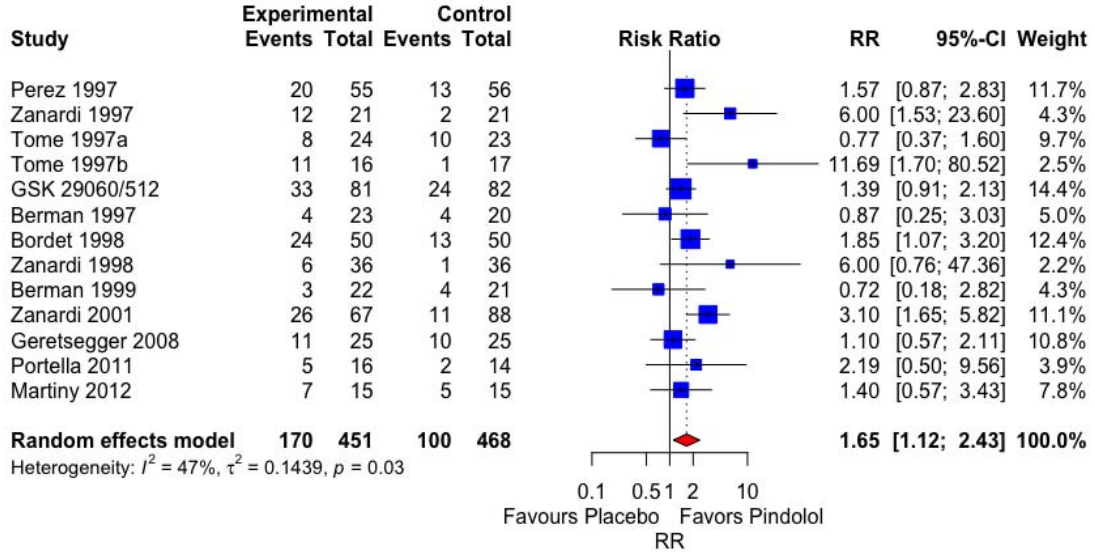

Figure 1. Forest plot. Random effects pooled estimate of risk ratios in randomized trials of SSRI+ pindolol versus SSRI+ placebo for early response (two week). The colored squares are proportional to individual study weights. Study references (Berman et al., 1997, Perez et al., 1997, Tome et al., 1997, Zanardi et al., 1997a, Bordet et al., 1998, Zanardi et al., 1998, Berman et al., 1999, Zanardi et al., 2001, Geretsegger et al., 2008, Whale et al., 2010, Portella et al., 2011, Martiny et al., 2012) and detailed description of data treatment from the studies included are described in Portella et al (Portella et al., 2011). RR is relative risk (95% CI)

b. Data were from one of the centers included at Tome et al(Tome et al., 1997)

c. Data were from the second center included at Tome et al (Tome et al., 1997)

GSK 29060/512 was published at Whale et al (Whale et al., 2010).

11. Discussió

El resultat dels estudis realitzats en aquesta tesi indiquen que el pindolol, un fàrmac **antagonista parcial** 5-HT1A, **accelera** i **augmenta** la resposta al tractament antidepressiu. Les dades es confirmen amb la metaanàlisi que estudia l'eficàcia en dos moments del tractament: a les 2 setmanes -que consideraríem una millora precoç dels símptomes- i a les 4-6 setmanes que és quan habitualment comencen a fer efecte els antidepressius.

Però per altra banda el DU125530, un **antagonista complet** 5-HT1A, no augmenta ni accelera la resposta del tractament antidepressiu.

Aquesta discrepància en els resultats pot ser deguda a diversos factors que es discutiran a continuació:

1) Acció del DU125530 i el pindolol sobre els receptors 5-HT1A presinàptics i postsinàptics
2) Importància de l'acció preferencial sobre el receptor 5-HT1A presinàptic per la potenciació del tractament antidepressiu
3) El paper de l'agonisme 5-HT1A en l'acció antidepressiva i l'estratègia de potenciació
4) La latència de resposta dels fàrmacs antidepressius monoaminèrgics i l'eficàcia del bloqueig del receptor 5-HT1A en l'escurçament de la resposta antidepressiva
5) Eficàcia del pindolol i de l'estratègia del bloqueig del receptor 5-HT1A presinàptic en les diferents poblacions de pacients depressius
6) Influència de les dosis de pindolol utilitzades per la potenciació del tractament antidepressiu
7) La influència de l'efecte β-blocant del pindolol
8) Factors farmacocinètics dels assajos clínics que poden influir en el resultat de l'estratègia de potenciació.
9) La utilitat del tractament antidepressiu endovenós
10) Aspectes metodològics dels assajos clínics

En la discussió també s'abordarà:

11) Us clínic del pindolol
12) Limitacions dels estudis
13) Paper del receptor 5-HT1A implicacions pel futur del tractament antidepressiu.

1) Acció sobre els receptors 5-HT1A presinàptics i postsinàptics del DU i el pindolol

L'estudi realitzat amb DU125530 amb resultat negatiu, probablement s'expliqui perquè aquesta molècula té un perfil farmacològic una mica diferent del pindolol. **El pindolol** té una major afinitat pels receptors serotoninèrgics 5-HT1A presinàptics que pels postsinàptics. Per tant la seva acció principal es realitza majoritàriament sobre dels receptors 5-HT1A somatodendrítics, situats a nivell presinàptic (Artigas et al., 1996b, Artigas et al., 2001). Cal tenir en compte que quan donem un ISRS, el bloqueig de la recaptació de serotonina que es produeix causa un augment important de serotonina al rafe, que és on hi ha major concentració de recaptador de 5-HT (Artigas et al., 1996a, Newberg et al., 2004). Aquest augment sobtat i important activa els mecanismes que té la neurona serotoninèrgica per evitar que es sobreexciti. S'activen els receptors 5-HT1A somatodendrítics que actuen com una vàlvula de seguretat i inhibeixen la neurona serotoninèrgica causant un descens de l'alliberació de serotonina a nivell terminal (Artigas et al., 1996a). El pindolol actuaria sobre aquest circuit de feed-back negatiu que presenta la neurona serotoninèrgica, bloquejant el 5-HT1A permetent una activació de la neurona serotoninèrgica més ràpida i produint un major alliberament de serotonina a nivell cortical (Artigas et al., 1996b).

El DU125530 presenta un perfil d'afinitat receptorial diferent. Bloqueja amb la mateixa afinitat els receptors presinàptics que els postsinàptics. Per tant, per una banda també interfereix en l'acció del receptor 5-HT1A a nivell presinàptic cancel·lant el circuit de retroalimentació negatiu, com es pot observar en els diversos experiments preclínics que s'adjunten amb la tesi. Per altra banda però, també bloqueja els receptors 5HT1A postsinàptics i això semblaria ser el factor diferencial entre un fàrmac i l'altre.

El bloqueig dels receptors 5-HT1A postsinàptics per part del DU125530 anul·laria l'acció beneficiosa del bloqueig presinàptic. Els receptors 5-HT1A postsinàptics es troben en neurones corticals, sobretot al còrtex prefrontal, en neurones piramidals i també gabaèrgiques (Santana et al., 2004, Sharp et al., 2007, Hornung, 2010). En ratolins s'ha observat que aquestes neurones controlen de manera distal la funció dels nuclis subcorticals, com els nuclis monoaminèrgics (Celada et al., 2013) i que l'activació dels receptors 5-HT1A modularia la funció dels nuclis del tronc de l'encèfal (Celada et al., 2001). S'ha trobat que l'estimulació dels receptors 5-HT1A postsinàptics a nivell cortical augmenta l'alliberació de catecolamines a nivell cortical i això semblaria un efecte necessari per l'acció terapèutica dels antidepressius (Haddjeri et al., 1998, Diaz-Mataix et al., 2005, Samuels et al., 2015b). També s'ha observat que el tractament crònic amb antidepressius causa una activació tònica dels receptors 5-HT1A hipocampals (Haddjeri et al., 1998, Blier and Ward, 2003) i que l'activació dels receptors 5-HT1A a nivell del gyrus dentat de l'hipocamp n'augmenta la neurogènesi (Jacobs et al., 2000).

També els receptors 5-HT1A tenen diferents capacitats funcionals en funció de la localització. Semblaria que els receptors 5-HT1A presinàptics tenen més facilitat per presentar processos adaptatius, com la dessensibilització i la regulació a la baixa, com s'ha observat en diversos estudis preclínics (Blier and de Montigny, 1994, Hervas et al., 2001). Per tant és més probable que els fàrmacs amb una preferència d'acció sobre els 5-HT1A presinàptic tinguin una major influència a aquest nivell i no a nivell postsinàptic.

Els estudis de neuroimatge en humans ens mostren que el pindolol a les dosis clíniques utilitzades produeix una major ocupació dels receptors 5-HT1A presinàptics que els 5-HT1A postsinàptics (Martinez et al., 2000, Rabiner et al., 2000a, Rabiner et al., 2000b, Martinez et al., 2001). En un estudi de PET realitzat en voluntaris sans i DU125530, s'observa que produeix una ocupació similar tant dels receptors 5-HT1A presinàptics com postsinàptics (Rabiner et al., 2002). Així en humans també s'observarien aquestes diferències en l'afinitat del DU125530 i el pindolol pel receptor 5-HT1A presinàptic i postsinàptic.

Per tant el fet d'obtenir un resultat negatiu en l'estudi del DU125530 i en canvi un resultat positiu en l'estudi del pindolol probablement sigui degut a que el DU125530 sigui un antagonista complet amb igual afinitat pels receptors presinàptics que pels postsinàptics. Per tant el bloqueig dels receptors 5-HT1A postsinàptics contrarestaria els beneficis de bloquejar el circuit de feed-back de la neurona serotoninèrgica. Això indicaria que per obtenir una resposta antidepressiva caldria que el receptor 5-HT1A a nivell cortical estigués activat.

2) Importància de l'acció preferencial sobre el receptor 5-HT1A presinàptic per a la potenciació del tractament antidepressiu.

Atès que el receptor 5-HT1A postsinàptic té un paper limitant per la resposta antidepressiva dels antidepressius monoaminèrgics (Haddjeri et al., 1998, Samuels et al., 2015a), el seu bloqueig o només una activació parcial podria ser perjudicial en una estratègia de millora del tractament. Per tant accelerar o augmentar la resposta antidepressiva dels fàrmacs monoaminèrgics passaria per bloquejar o dessensibilitzar el receptor 5-HT1A presinàptic i activar, o com a mínim no bloquejar ni disminuir de cap manera l'activitat del receptor 5-HT1A postsinàptic.

Una estratègia recentment desenvolupada seguint aquesta línia de recerca és la utilització dels siRNA (small-interfering RNA). Són fragments de RNA que s'administren juntament amb un ISRS. Aquestes sondes de RNA-ISRS es desplacen fins al rafe, perquè allà és on hi ha major concentració de transportador de 5-HT (Cortes et al., 1988) i l'associació amb un ISRS el dirigeix cap allí. Al rafe causa un bloqueig o interferència de l'expressió dels receptor 5-HT1A en les neurones serotoninèrgiques obtenint respostes antidepressives importants en models animals

de depressió (Bortolozzi et al., 2012b, Ferres-Coy et al., 2012). Amb aquesta estratègia es bloqueja selectivament el receptor serotoninèrgic 5-HT1A presinàptic i alhora no s'altera la funcionalitat del receptor 5-HT1A postsinàptic.

El pindolol, segons els estudis experimentals, no sembla modificar l'activitat del receptor 5-HT1A a nivell postsinàptic. Quan es co-administra amb un agonista complet, el pindolol no en reverteix l'efecte i per tant l'acció principalment la realitza a nivell del rafe, sobre el receptor 5-HT1A presinàptic (Romero et al., 1996).

En resum, el pindolol actua principalment a nivell presinàptic i d'aquí el seu potencial benefici en l'estratègia de potenciació del tractament antidepressiu.

3) El paper de l'agonisme 5-HT1A en la resposta antidepressiva

El resultat negatiu amb l'estudi del DU125530, que és un antagonista complet, i en canvi positiu amb el pindolol, que és un antagonista parcial, porta a preguntar-nos si la potenciació del tractament antidepressiu per part del pindolol és mediada, en part, per una possible acció agonista parcial sobre el receptor 5-HT1A.

S'ha discutit si el pindolol podia tenir una acció agonista parcial i si aquest agonisme parcial podria ser responsable de l'acció antidepressiva del fàrmac (Artigas et al., 2001). El pindolol in vitro presenta una acció agonista intrínseca (Newman-Tancredi et al., 1998) i en alguns models experimentals es comporta com un agonista parcial i en altres com un antagonista parcial. Això segurament és degut a la complexitat de l'agonisme/antagonisme parcial, que dificulta la interpretació dels resultats quan es modifiquen les condicions ambientals de l'experiment. Es a dir, es comporta com a agonista o antagonista en funció de si s'administra amb un agonista complet o amb un antagonista complet, o amb un ISRS que produeix un augment de serotonina brusc, o si s'administra tot sol (Artigas et al., 2001).

Sembla però, que els resultats d'experiments que simulen el que deu passar en el cervell quan s'administra el pindolol amb un antidepressiu serotoninèrgic, indicarien que el pindolol es comporta com un antagonista parcial. El pindolol és capaç de revertir la inhibició de les neurones serotoninèrgiques produïda per un ISRS i augmentar la serotonina extracel·lular a nivell cortical mitjançant la seva interacció amb el receptor 5-HT1A presinàptic (Romero et al., 1996).

Per altra banda la interacció del pindolol amb el receptor 5-HT1A postsinàptic podria tenir un paper en la resposta antidepressiva al ser un agonista/antagonista parcial. Quan s'intenta estudiar el seu paper a nivell experimental en persones és complicat i difícil d'interpretar-ne els resultats.

Fins al moment actual els agonistes 5-HT1A desenvolupats per l'ús humà son agonistes parcials (els agonistes complets són mal tolerats degut als efectes secundaris (Grof et al., 1993)). Les azapirones són fàrmacs agonistes parcials dels receptors 5-HT1A. Són medicaments amb una eficàcia limitada

com a antidepressius i presenten problemes de tolerància importants (Kishi et al., 2014). Quan són administrades, no tindrien una acció agonista completa sobre els receptors 5-HT1A postsinàptics. Sota condicions d'augment de serotonina (per exemple quan administrem un tractament antidepressiu i augmenta l'alliberament de serotonina a nivell cortical), llavors els agonistes parcials es comportaran interferint en l'estimulació produïda per la serotonina endògena. D'aquesta manera els agonistes parcials es comportarien bloquejant parcialment l'acció de la serotonina endògena ja que produiria una estimulació menys eficient del receptor 5-HT1A (Celada et al., 2013). Per altra banda l'acció agonista sobre els 5-HT1A presinàptics provoca la disminució d'alliberació de serotonina, ja que l'acció resultant sobre els 5-HT1A presinàptics és una inhibició de la neurona serotoninèrgica. El tractament crònic amb azapirones causaria una dessensibilització del receptor, com passa quan s'administra un ISRS i augmenta la serotonina extracel·lular (Blier and Ward, 2003). De fet, quan s'administra de manera aguda ISRS i azapirones no es genera un augment de serotonina a nivell cortical, cosa que sí que succeeix quan s'administra el pindolol amb un ISRS (Hjorth, 1996).

En els models experimentals però, quan s'utilitzen dosis altes d'azapirones s'observa un efecte antidepressiu, possiblement degut a l'efecte d'activació del receptor 5-HT1A postsinàptic per part de les azapirones. Però en persones s'han d'usar dosis més baixes i llavors al competir amb la serotonina endògena causa una estimulació del receptor 5-HT1A postsinàptic menys eficaç (Artigas, 2013).

Pel que fa al mecanisme d'acció de les azapirones, aquest és força obscur. D'una banda es metabolitzen ràpidament en un compost que té accions antagonistes del receptor alfa 2 generant dificultats alhora d'interpretar el mecanisme d'acció (Celada et al., 2013). Per altra banda també té una acció antagonista parcial D2 i per tant ajuda poc a discernir entre el paper del receptor 5-HT1A en el tractament de la depressió.

En resum podem dir que el receptor 5-HT1A està íntimament implicat en la resposta antidepressiva i la seva activació és necessària per què s'aconsegueixi l'efecte antidepressiu amb els fàrmacs que actuen modulant les monoamines.

4) La latència de resposta dels fàrmacs antidepressius monoaminèrgics i l'eficàcia del bloqueig del receptor 5-HT1A per l'escurçament de la resposta antidepressiva

Els antidepressius monoaminèrgics són lents en el seu mecanisme d'acció i aquesta és una de les principals limitacions a l'hora de tractar la depressió.

Els darrers anys, arrel de l'observació dels efectes de la ketamina, que origina una millora molt ràpida dels símptomes depressius (en hores), la recerca científica s'ha centrat en intentar produir fàrmacs que actuïn a través dels receptors glutamatèrgics. Els resultats inicials que

resultaven molt esperançadors amb la ketamina no s'han materialitzat en nous fàrmacs antidepressius. Diverses molècules que actuen com a moduladors del receptor glutamatèrgic no han resultat eficaces pel tractament de la depressió quan s'han provat en assajos clínics (Caddy et al., 2015). Sembla que només la ketamina obté resultats robustos principalment a curt termini (1 setmana) amb l'inconvenient que els efectes secundaris que presenta no són banals (Caddy et al., 2015). Per aquestes característiques, de moment sembla reservada per pacients resistents i amb risc de suïcidi (Andrade, 2017). També cal tenir en compte els potencials riscs d'abús, ja que és una de les principals substancies d'abús al continent asiàtic i no hi ha dades de la seguretat del medicament a mig i llarg termini.

Per tant, actualment a nivell de pràctica clínica, els principals tractaments antidepressius disponibles son aquells que actuen sobre els sistema monoaminèrgic. Son fàrmacs segurs, dels que en coneixem els efectes a curt, mig i llarg termini en una població àmplia i diversa de pacients deprimits. Són usats àmpliament i amb confiança per atenció primària i han permès avançar molt en el tractament de la depressió, tenint un impacte inclús en les taxes de suïcidi (Gibbons et al., 2005, Kalmar et al., 2008). Per tant les estratègies que puguin disminuir el temps de latència i augmentar l'eficàcia dels antidepressius monoaminèrgics són plenament vigents.

El pindolol, ha resultat una estratègia eficaç a l'hora d'escurçar la latència de resposta dels antidepressius. En el nostre estudi de pindolol vs placebo amb citalopram pel tractament de la depressió major va resultar eficaç a l'hora d'escurçar el temps d'inici de la resposta antidepressiva.

Els assaigs on es va estudiar la capacitat del pindolol per **accelerar la resposta** van ser clarament positius, mostrant un clar efecte del pindolol sobre l'inici de la resposta, escurçant la latència dels antidepressius. En 9 dels 12 estudis, incloent el que forma part d'aquesta tesi, on s'estudiava aquesta capacitat, es mostrava una acceleració de l'inici de resposta (Perez et al., 1997, Tome et al., 1997, Zanardi et al., 1997a, Bordet et al., 1998, Zanardi et al., 1998, Shiah et al., 2000, Isaac et al., 2003, Geretsegger et al., 2008, Portella et al., 2011). En un estudi únicament es va detectar aquest efecte en un dels centres participants (Tome et al., 1997) i hi ha tres estudis amb resultat negatiu (Berman et al., 1997, Berman et al., 1999, Whale et al., 2010). En dos dels estudis amb resultats negatius, els autors descriuen que a la mostra hi havia molts pacients amb tendència a presentar cronicitat i recurrències. En un altre estudi, l'acceleració de resposta només es produeix en aquells pacients amb depressió bipolar (Geretsegger et al., 2008).

En l'estudi de metaanàlisi presentat en aquesta tesi, utilitzant les dades dels estudis realitzats en pacients amb depressió no resistent, mostren que els pacients que inicien un tractament antidepressiu amb un ISRS es beneficien de l'estratègia de potenciació amb pindolol. Aquests mostren una resposta més ràpida als antidepressius.

En el moment actual hi ha diversos nous antidepressius que actuen sobre el sistema monoaminèrgic i que s'han desenvolupat perquè tinguessin una afinitat parcial pel receptor 5-HT1A per tal de millorar-ne l'eficàcia. La v**ilazodona** i la **vortioxetina** són dos exemples de fàrmacs que presenten agonisme parcial del receptor 5-HT1A i actuen en part, dessensibilitzant el receptor 5-HT1A. La vilazodona, encara no comercialitzada al nostre país, és un fàrmac que actua inhibint la recaptació de serotonina i presenta un agonisme parcial 5-HT1A. La Vortioxetina ja comercialitzada aquí, té també acció inhibidora de la recaptació de serotonina, un agonisme parcial 5-HT1A i també té afinitat però per molts altres receptors serotoninèrgics 5-HT3, 5-HT1B, 5-HT1D i 5-HT7 (Sanchez et al., 2015). La vilazodona però no sembla un fàrmac que aporti importants avantatges respecte als ISRS, ni major rapidesa ni major eficàcia (Sahli et al., 2016). En canvi la vortioxetina sembla que presenta resultats més interessants a nivell clínic, amb una eficàcia similar o no inferior a la venlafaxina (Thase et al., 2016).

En el cas de la vilazodona podria ser que els possibles efectes beneficiosos obtinguts de dessensibilitzar el receptor 5-HT1A a nivell presinàptic i per tant disminuir el mecanisme de feed-back quedessin anul·lats o contrarestats per una menor eficàcia a l'hora d'estimular els receptors postsinàptics i això en limités l'eficàcia antidepressiva. El nostre estudi amb DU125530 mostra que si es produeix un bloqueig dels receptors 5-HT1A a nivell postsinàptic la potenciació antidepressiva del ISRS no es produeix, indicant que és necessària una activació dels 5-HT1A postsinàptics per observar-ne l'efecte positiu. La vilazodona a dosis més altes, en els estudis preclínics amb animals, no produeix un efecte antidepressiu i això podria ser degut a que al presentar agonisme parcial produís una menor activació del 5-HT1A que la serotonina endògena i per tant es cancel·lés l'efecte beneficiós (Page et al., 2002).

Probablement el perfil farmacològic singular del pindolol fa que sigui aquest fàrmac el que escurci i potenciï els efectes dels ISRS: l'equilibri entre la dessensibilització del receptor 5-HT1A a nivell presinàptic i la baixa interacció amb el receptor 5-HT1A postsinàptic a nivell cortical juntament amb el seu antagonisme/agonisme parcial.

Com a conclusió podem extreure que el pindolol escurça la latència de resposta dels antidepressius serotoninèrgics però altres antidepressius com la vilazodona i la vortioxetina que actuen dessensibilitzant el receptor 5-HT1A presinàptic aquest efecte no es veu. Probablement aquest fet sigui degut al perfil d'afinitat singular que presenta el pindolol amb una preferència d'acció sobre el receptor 5-HT1A presinàptic.

5) Eficàcia del pindolol i de l'estratègia del bloqueig del receptor 5-HT1A presinàptic en les diferents poblacions de pacients depressius

El resultat de l'estudi amb pindolol que presenta aquesta tesi, aporta més evidència sobre la utilitat del pindolol pel tractament de la depressió major, tant per accelerar la resposta com per augmentar-la. En canvi el DU125530 no ha resultat cap avantatge respecte al placebo, segurament pel diferent perfil d'afinitat que presenta aquesta molècula.

Tal i com s'exposa a la tesi, sembla que en pacients amb **depressió no resistent** al tractament antidepressiu, el pindolol pot ser una estratègia útil en el tractament coadjuvant de la depressió. Resulta útil tant per escurçar-ne la resposta antidepressiva com per augmentar-la.

S'havien publicat dues metaanàlisis que estudiaven la utilitat del pindolol com a estratègia de potenciació antidepressiva (Ballesteros and Callado, 2004, Whale et al., 2010). Totes dues concloïen que la combinació d'un antidepressiu amb el pindolol tenia un clar avantatge respecte al tractament amb l'antidepressiu sol. El pindolol augmentava la resposta sobretot les primeres setmanes de tractament (fins la quarta). A la sisena setmana semblava que l'efecte es perdia.

La metaanàlisi realitzada pel nostre grup va ampliar el numero d'estudis i afegir les dades de l'estudi realitzat pel nostre grup. Es van demanar dades addicionals als autors dels estudis de la resposta als dos temps de tractament: a les dues setmanes d'haver-se iniciat el tractament i a les 4-6 setmanes, ja que s'havia observat que alguns estudis obtenien una resposta inicial que després es perdia. El resultat de la nostra metaanàlisi va confirmar que el pindolol va resultar una estratègia útil per la potenciació del tractament a les 2 setmanes (de manera precoç) i a les 4-6 setmanes.

Per altra banda, analitzant els estudis previs realitzats amb pindolol per potenciar el tractament antidepressiu, s'observen resultats en funció de la mostra de pacients, si aquests són resistents al tractament antidepressiu o no.

Hi ha quatre estudis realitzats en pacients que presentaven **depressió resistent**, definida aquesta amb el criteri de no resposta com a mínim a un antidepressiu per l'episodi actual. En tres d'ells, el pindolol no resulta útil per augmentar ni accelerar la resposta al tractament (Moreno et al., 1997, Perez et al., 1999, Perry et al., 2004). Sokolski et al (Sokolski et al., 2004) en una mostra de 9 pacients sí troben diferències respecte el placebo però la mostra és molt petita.

La majoria d'estudis realitzats amb pindolol inclouen **mostres mixtes de pacients**, amb pacients lliures de tractament i pacients amb resistència al tractament que tenen resultats variables a l'hora d'augmentar el tractament, però a l'hora d'accelerar la resposta, els resultats semblen més robustos.

En molts assajos clínics, tot i no ser definida la mostra de pacients amb depressió resistent exclusivament, es van incloure pacients que segurament presentessin resistència al tractament antidepressiu. Per exemple aquells pacients que ja havien rebut tractament antidepressiu per l'episodi actual i eren inclosos a l'estudi. Hi ha diversos estudis amb resultats negatius pel pindolol en quant a augmentar la resposta antidepressiva que probablement van incloure molts pacients refractaris: per exemple en l'estudi de Berman (Berman et al., 1999) només una quarta part dels pacients no havien pres tractament antidepressiu anteriorment. En el de Tome (Tome et al., 1997), que es realitza en dos centres alhora, en el centre amb resultats negatius observen que el 50% de pacients ja havien estat tractats per l'episodi actual amb antidepressius. Els pacients dels estudis de Geretsegger (Geretsegger et al., 2008) i Martiny (Martiny et al., 2012) en més de la meitat dels casos havien pres tractament per l'episodi actual de depressió.

També hi ha estudis que al descriure la mostra expliquen que inclouen pacients amb depressió cronificada o recurrències (Berman et al., 1997, Geretsegger et al., 2008, Martiny et al., 2012), característiques que solen associar-se a una resposta pobra al tractament (Trivedi et al., 2006, Warden et al., 2007).

La inclusió de pacients amb resistència al tractament antidepressiu previ, o amb molts antecedents de recurrències i depressions cronificades podria explicar part de la variabilitat en els resultats dels estudis.

Dos autors detecten que l'estratègia de potenciació amb el pindolol obté millors resultats en pacients que no havien pres mai tractament antidepressiu i en pacients que presentaven un primer episodi depressiu. Es detecta inclús una resposta més ràpida en aquest darrer grup de pacients (Geretsegger et al., 2008) (Portella et al., 2009).

Aquestes dades van suggerir que la resistència farmacològica als antidepressius podria ser un factor de **no resposta** al pindolol. Per aquest motiu es va decidir no incloure pacients resistents al tractament en els nostres estudis. Ni en l'estudi de pindolol vs placebo i citalopram ni en l'estudi del DU125530 vs placebo i fluoxetina hi ha inclosos pacients resistents.

Els pacients provenien principalment d'atenció primària i d'urgències de psiquiatria. Un dels criteris d'exclusió per participar en els assajos era la resistència al tractament antidepressiu, tant en episodis passats com en l'episodi actual, definida com a no resposta a un tractament antidepressiu correcte. En l'estudi de citalopram s'excloïen pacients amb antecedents d'haver presentat resistència al citalopram en el passat i en l'estudi del DU125530 el criteri era més estricte, demanant-se l'absència de resistència a qualsevol antidepressiu en el passat.

Els pacients dels nostres estudis, majoritàriament eren pacients sense història d'episodis previs depressius: en l'estudi amb pindolol el 60% de pacients presentaven el primer episodi depressiu, en el cas del DU125530, la proporció és lleugerament menor, essent el 50% dels pacients. També la mitjana de durada dels episodis depressius dels pacients dels estudis no fa pensar en que la

cronicitat sigui un factor que hagi interferit en els resultats. El 60% dels pacients que van participar en l'estudi del DU125530 presentaven una durada de l'episodi d'un a sis mesos i en el cas del citalopram només tres pacients presentaven una durada de l'episodi depressiu de més de 6 mesos (mostra més petita).

L'estudi de potenciació del tractament amb pindolol va donar resultats positius i en canvi l'estudi utilitzant el DU125530 no. Tenint en compte que la població mostral era la mateixa i amb característiques similars, no es poden atribuir les diferències a una mostra amb més resistència farmacològica. Per tant es reforça la hipòtesi que el diferent perfil d'afinitat receptorial del DU125530 és el que fa que no sigui una estratègia eficaç per la potenciació dels ISRS.

En resum, observem que l'estratègia de potenciació del tractament antidepressiu mitjançant antagonistes del receptor 5-HT1A resulta principalment eficaç en la població de pacients depressius no resistents al tractament antidepressiu.

Altres variables clíniques:

Els nostres estudis no van mostrar que la presència de depressió recurrent o la durada de l'episodi tingués cap influència en la resposta al pindolol o al DU125530. Tampoc la presència de melancolia en cap dels dos estudis es va associar a una millor resposta al pindolol o al DU125530. Altres estudis realitzats amb pindolol també valoren aquesta possibilitat i descarten cap relació entre aquests factors clínics i els resultats amb pindolol (Maes et al., 1996, Berman et al., 1997, Zanardi et al., 1998, Maes et al., 1999). En l'estudi de Tomé et al (Tome et al., 1997), es descriu una relació inversa entre una millor resposta al pindolol i la presència de cronicitat. Aquest fet concorda amb la hipòtesis que la resistència antidepressiva sigui un factor de no resposta a l'estratègia de potenciació amb antagonistes 5-HT1A. Perez et al (Perez et al., 2001), observen significació marginal entre el temps de resposta sostinguda en pacients en tractament amb fluoxetina i placebo amb l'índex de Newcastle (Davidson et al., 1984). També observa una correlació marginal, positiva també, entre la durada de l'episodi actual i la resposta al pindolol en els pacients que van rebre pindolol i fluoxetina.

6) Influència de les dosis de pindolol utilitzades per la potenciació del tractament antidepressiu

En l'estudi de pindolol vs placebo i citalopram que es presenta en aquesta tesi s'utilitzen dosis més altes de les utilitzades anteriorment amb el pindolol (15 mg/dia). La majoria d'estudis realitzats anteriorment utilitzen dosis de 7.5 mg/dia.

Els estudis de neuroimatge permetien observar l'ocupació del receptor 5-HT1A en humans en viu. Es va observar que la dosi habitual de pindolol de 7.5 mg/dia produïa una ocupació dels

receptors 5-HT1A molt baixa a nivell del rafe (Rabiner et al., 2001). Es va postular la necessitat d'augmentar les dosis per arribar a una ocupació suficient per aconseguir tenir un efecte clínic i bloquejar el circuit de retroalimentació negatiu al rafe mediat pel receptor 5-HT1A somatodendrític.

El nostre estudi es va realitzar amb dosis més altes de pindolol, de 15 mg/dia, i es va obtenir un resultat positiu en quant a l'eficàcia. Bordet et al també utilitzen dosis de 15 mg/dia amb resultats a favor del pindolol en l'inici de la resposta antidepressiva (Bordet et al., 1998). En canvi Martiny (Martiny et al., 2012) utilitza la dosi de 20 mg/dia i no obté un resultat a favor del pindolol. El mateix autor explica que la seva mostra de pacients presentava un alt percentatge de refractarietat i aquest podia ser el motiu pel que, tot i amb dosis més altes, el pindolol no fos eficaç. Un altre estudi utilitzant dosis no tan altes, de 7.5 a 10 mg/dia, també tenia resultats negatius (Berman et al., 1999). Seria possible que una dosi excessivament elevada de pindolol acabés resultant en un bloqueig del receptor 5-HT1A postsinàptic anul·lant-ne així l'efecte beneficiós. De fet, els estudis de neuroimatge mostren un blocatge dosi dependent proporcional tot i que amb predomini pel rafe (Martinez et al., 2000). És a dir, a dosis més altes de pindolol augmenta el bloqueig tant del receptor 5-HT1A presinàptic com del postsinàptic. Tot i això, el pindolol presenta una major afinitat pels receptors 5-HT1A del rafe que pels receptors 5-HT1A situats a nivell cortical, fet que fa pensar que predominaria l'acció sobre el rafe i la neurona serotoninèrgica i que per tant dosis altes de pindolol tindrien poc efecte a nivell cortical.

En resum, podem dir que dosis més altes de pindolol han resultat eficaces per potenciar el tractament antidepressiu i accelerar-ne la resposta. Aquestes dosis més altes no semblen interferir en l'activació del receptor 5-HT1A degut a una major preferència del pindolol pels receptor 5-HT1A presinàptics.

7) La influència de l'efecte β-blocant del pindolol

Un aspecte a tenir present és que el pindolol no té únicament afinitat pel receptor serotoninèrgic 5-HT1A sinó que també és un fàrmac antagonista dels receptors β-adrenèrgics. Tot i això no és un fàrmac amb molta potència com a β-blocant, motiu pel qual ha anat caient en desús a nivell cardíac quan s'han anat desenvolupant altres β-blocants més efectius i potents.

Les primeres observacions sobre els efectes dels antidepressius van posar de manifest que alguns d'ells regulaven a la baixa l'expressió dels receptors β-adrenèrgics (ISRS i tricíclics) (Byerley et al., 1988). Es va pensar per tant que potser el pindolol podria actuar regulant a la baixa aquests receptors però semblaria més un efecte colateral que no el principal mecanisme d'acció dels antidepressius, ja que no tots els antidepressius ho produeixen. Posteriorment es va observar que els β-blocants s'associaven a major incidència de depressió (Avorn et al., 1986).

Per tant semblaria que seria la seva afinitat pel receptor 5-HT1A serotoninèrgic la responsable dels efectes beneficiosos sobre el tractament antidepressiu i no el seu efecte sobre els receptors β-adrenèrgics.

També es va postular si el pindolol, en la seva acció β-blocant, podria tenir un efecte ansiolític i això confongués a l'hora d'interpretar els resultats, ja que els β-blocants s'han fet servir en alguns trastorns d'ansietat com la fòbia social per disminuir els efectes fisiològics de l'ansietat. En alguns estudis es va realitzar una anàlisi de les subescales de la HDRS que descriuen l'ansietat i no es va trobar relació amb l'eficàcia del pindolol. Al contrari, detecten que les millores es donen en les subescales dels ítems més pròpiament depressius (Perez et al., 1997) (Bordet et al., 1998, Maes et al., 1999). Tampoc en el nostre estudi hi ha relació entre l'eficàcia i els ítems d'ansietat (ítem 10 i 11 de l'escala de Hamilton $p>0.05$)

L'afectació de les constants vitals, que podria ser un reflex de l'acció β-blocant, tampoc es relaciona amb l'efectivitat del fàrmac segons he revisat. Per altra banda, en un assaig clínic pel tractament de la depressió, es va utilitzar el metropolol, un β-blocant sense afinitat pels receptors 5-HT1A i es va observar que no tenia efectes sobre el tractament de la depressió (Zanardi et al., 1997a). Per tant sembla excloure's del tot la possibilitat que l'efecte β-blocant del pindolol tingui alguna relació amb l'efectivitat del pindolol.

Existiria el risc, si s'usessin dosis molt altes de pindolol, d'acabar presentant un efecte β -blocant amb efectes negatius pel tractament de la depressió, però en el nostre estudi, a dosis de 15 mg/dia, no sembla que això s'hagi produït. Cal tenir en compte però, que el rang de dosi del pindolol d'ús a nivell cardiològic solia anar dels 5 als 30 mg/dia.

Per tant segons les dades del nostre estudi i revisant els estudis publicats no sembla que l'efecte β-blocant del pindolol sigui rellevant a l'hora de valorar l'efecte de potenciació antidepressiva.

8) Factors farmacocinètics dels assajos clínics que poden influir en el resultat de l'estratègia de potenciació

Sembla que els **nivells plasmàtics dels antidepressius** no tenen una clara relació amb la resposta antidepressiva en general, probablement degut a que la resposta antidepressiva és complexa i calen molts passos posteriors a l'arribada del fàrmac a la sang perquè pugui fer l'efecte clínic (Perry et al., 1994, Perucca et al., 1994, Amsterdam et al., 1997). S'ha estudiat també si factors genètics que modulen la metabolització dels antidepressius podrien influir en els nivells plasmàtics i la resposta. S'ha observat que variacions genètiques dels gens que codifiquen els enzims del citocrom P450 (responsables de la metabolització de molts antidepressius) es correlacionen amb variacions dels nivells plasmàtics però no amb la resposta dels antidepressius (Hodgson et al., 2014). Per altra banda recentment s'ha detectat que variacions al·lèliques del

gen que codifica la glicoproteïna P (que transporta alguns antidepressius dins el cervell) té relació amb els nivells plasmàtics i la resposta antidepressiva (Breitenstein et al., 2016).

En el moment actual la determinació de nivells plasmàtics dels antidepressius únicament és d'utilitat per observar el compliment terapèutic del tractament (Laux et al., 2007).

En tres dels assajos clínics realitzats amb pindolol es van determinar nivells plasmàtics d'antidepressius. En cap d'ells es va observar relació entre la resposta antidepressiva i el nivells plasmàtics. En el de Pérez et al (Perez et al., 2001), realitzat amb fluoxetina, els nivells de fluoxetina i norfluoxetina van anar augmentant progressivament fins a la setmana 4, d'acord amb les dades d'estudis anteriors, i no es van trobar diferències entre pacients que responien i que no responien. En el de Zanardi et al (Zanardi et al., 1998), realitzat amb fluvoxamina, tampoc observen que hi hagi una relació entre els nivells plasmàtics i la resposta antidepressiva. En el de Martiny (Martiny et al., 2012) tampoc troben relació entre la resposta antidepressiva i el quocient ODV/V que es un quocient entre un metabòlit actiu de la venlafaxina amb afinitat pel transportador de serotonina i noradrenalina i la venlafaxina.

En el nostre estudi realitzat amb citalopram i pindolol vs placebo es van determinar els nivells plasmàtics de citalopram al dia 3 (després del tractament endovenós) i al dia 42 (al final de l'estudi). No es van trobar diferències significatives entre els nivells plasmàtics de citalopram el dia 3 i el dia 42. Tampoc no hi havia diferències entre grups quan els nivells plasmàtics eren comparats longitudinalment, obtenint-se nivells estables des de l'inici del tractament a diferència per exemple de la fluoxetina que requeria algunes setmanes fins aconseguir nivells estables. Tampoc no hi havia relació entre la resposta clínica al final de l'estudi entre els nivells plasmàtics de citalopram el dia 3 ni el dia 42.

En l'estudi de DU15530 vs placebo es van determinar els nivells de fluoxetina al dia 14 (a les 2 setmanes d'estar prenent el tractament) i al dia 42 (final de l'estudi). La concentració plasmàtica de fluoxetina al dia 14 i al dia 42 no diferia entre els grups. Tampoc no hi havia relació entre la resposta clínica al final de l'estudi i els nivells plasmàtics d'antidepressiu al dia 14 i al dia 42.

Per tant la interacció del pindolol o el DU125530 amb els nivells plasmàtics dels antidepressius no sembla explicar la diferència en quant a la resposta antidepressiva.

En quant als nivells plasmàtics de pindolol, tres estudis han realitzat determinacions plasmàtiques dels nivells de pindolol: Pérez et al en l'estudi pel tractament de la depressió major (Perez et al., 2001) i en l'estudi del tractament de la depressió resistent (Perez et al., 1999) i posteriorment Martiny (Martiny et al., 2012). Únicament en el primer estudi es va trobar que la mitjana de pindolol en pacients que responien era més baixa en que els que no responien. En l'estudi en depressió resistent no es va detectar diferència entre pacients que responien i que no responien. En l'estudi de Martiny, tampoc se'n va detectar. Únicament es va detectar un

efecte positiu del pindolol en el grup de pacients que son metabolitzadors lents de venlafaxina sense poder donar una explicació o significat d'aquesta troballa.

Per altra banda els nivells obtinguts de pindolol a dosi de 7.5 mg/dia en un estudi eren entre 6-7 ng/ml de mitjana (Perez et al., 2001), de 9,9 ng/ml en l'altre estudi (Perez et al., 1999) i es mantenien estable des de moments inicials del tractament (Perez et al., 2001, Martiny et al., 2012). En l'estudi de Martiny (Martiny et al., 2012) utilitzen dosis més altes de pindolol (20 mg/dia) obtenen nivells més elevats, al voltant de 29,8 ng/ml. Aquests darrers nivells plasmàtics són equivalents als trobats en l'estudi de neuroimatge de Rabiner (Rabiner et al., 2001) amb els quals obté uns nivells d'ocupació del 20% dels 5-HT1A presinàptics, una ocupació calculada per obtenir un bloqueig suficient dels 5-HT1A i aturar el mecanisme de feed-back negatiu serotoninèrgic. Tot i els nivells més alts de pindolol de l'estudi de Martiny, el resultat és negatiu i no hi ha diferències respecte al placebo. En aquest cas però la mostra de pacients presenta molts pacients refractaris amb el qual es fa difícil pensar que els nivells de pindolol tinguin a veure amb la resposta.

En els nostres estudis no vam poder determinar els nivells plasmàtics de pindolol ni de DU125530 per motius organitzatius i econòmics. El tenir-ne els resultats segurament completaria la informació prèvia i és una limitació dels estudis. Tot i així donats els resultats previs sembla poc probable que els nivells plasmàtics de pindolol siguin excessivament importants en la resposta al mateix.

9) La utilitat del tractament antidepressiu endovenós

En l'estudi de citalopram i pindolol vs placebo s'utilitza el citalopram endovenós que obté nivells plasmàtics al tercer dia de tractament, similars als del final de l'estudi. Es probable que el tractament endovenós hagi optimitzat la resposta antidepressiva. Existeixen estudis en els quals el tractament endovenós amb antidepressius tricíclics aconsegueix respostes més ràpides (Gastpar et al., 1986, Laux et al., 1989, Pollock et al., 1989, Deisenhammer et al., 2000). Aquesta major rapidesa en l'inici de l'acció podria ser deguda a diversos factors: per una banda s'evita l'incompliment del tractament, hi ha una menor pèrdua en l'absorció del medicament i no hi ha l'efecte de primer pas hepàtic. D'aquesta manera s'aconseguirien nivells plasmàtics d'antidepressiu més ràpids i elevats en sang. Els nivells més ràpids i alts podrien originar una major presència de concentració de l'antidepressiu al cervell i podria ajudar a evitar l'efecte de feedback negatiu a través de l'activació dels receptors serotoninèrgics 5-HT1A presinàptics. Uns nivells alts i ràpids de l'antidepressiu inicialment activarien el mecanisme de feedback però al persistir elevats de manera intensa continuarien bloquejant la recaptació de serotonina i per tant actuant sobre els receptors postsinàptics, realitzant l'acció antidepressiva. El mecanisme

d'autoregulació mediat pel receptor 5-HT1A quedaria desbordat per la presència elevada d'antidepressiu a l'espai sinàptic.

Hi ha dades recents de neuroimatge amb un compost nou [^{11}C]AZ10419369 que té afinitat pels receptors serotoninèrgics 5-HT1B que es desplaça per la serotonina endògena, fet que no succeeix amb els estudis realitzats amb [^{11}C]WAY100635. En els primats, si s'administra escitalopram a dosis altes endovenoses (2 mg/kg) s'observa com disminueixen els BP (llocs d'unió potencial) de 5-HT1B, indicant un desplaçament del lligand per la serotonina endògena i per tant indicant un augment de l'alliberament de serotonina endògena pel bloqueig del transportador de serotonina (Nord et al., 2013). En canvi en l'humà, amb una dosi d'escitalopram de 20 mg v.o. (equivalent a 0.25-0.3 mg/kg), dosi casi 10 vegades inferior a la utilitzada en els primats, s'obté un descens del BP en els nuclis del rafe (Nord et al., 2013), d'acord amb el que s'ha observat també en els models animals (Hervas and Artigas, 1998). Per altra banda l'escitalopram augmenta els BP a nivell cortical, indicant una reducció de la serotonina disponible ja que augmenten els llocs lliures de 5-HT1B pel radiolligand. Per tant aquestes observacions són concordants amb el mecanisme d'autoregulació de les neurones serotoninèrgiques mediat pels autoreceptors 5-HT1A i 5-HT1B observats en ratolins. Aquest estudi també indica que dosis altes d'antidepressius poden sobrepassar i desbordar els mecanismes d'autoregulació, ja que en primats, quan utilitzem dosis molt altes, aquest mecanisme queda desbordat.

El citalopram és l'únic antidepressiu ISRS disponible al mercat amb formulació endovenosa. Anteriorment s'havia realitzat un assaig clínic doble cec amb citalopram endovenós 40 mg/dia versus tractament oral durant la primera setmana de tractament, i es va observar que al final de l'estudi el descens de la MADRS era superior en els pacients que havien rebut tractament endovenós i també hi havia una millora més important en la ICG (Guelfi et al., 2000). En el nostre estudi tots els pacients rebien tractament endovenós els primers tres dies i presentaven llavors uns nivells plasmàtics que romanien estables fins al final de l'estudi (al voltant de 30 µg/l)

Per tant l'ús de citalopram endovenós podria ser una estratègia útil en el tractament inicial de la depressió tot i que la seva administració té dificultats evidents, com els requeriments d'administració del mateix tractament i per tant en limita l'ús pràctic.

El tractament endovenós en el nostre estudi va ser ben tolerat a excepció d'un pacient que es va haver de retirar per presentar efectes secundaris gastrointestinals. Aquest pacient en la seva evolució no va tolerar cap ISRS v.o. per presentar aquests mateixos efectes secundaris gastrointestinals, per tant segurament no era degut a l'administració endovenosa sinó al propi perfil farmacològic del citalopram.

10) Aspectes metodològics dels assajos clínics

Període de placebo inicial

En l'estudi de pindolol vs placebo i citalopram d'aquesta tesi no es va utilitzar fase de placebo. En l'anterior estudi realitzat pel nostre grup amb el pindolol sí es va utilitzar una fase inicial de placebo (Perez et al., 1997). La inclusió d'aquesta fase permet excloure pacients que responen ràpidament al placebo i que els resultats observats siguin atribuïts amb més veracitat als efectes dels psicofàrmacs. En aquell estudi es van incloure 132 pacients dels quals 19 van respondre al placebo i no van arribar a ser randomitzats. L'estudi va donar resultats positius a favor del pindolol amb una major resposta enfront al placebo. Posteriorment es van analitzar les dades de l'estudi i es va calcular si l'efecte s'hauria observat igualment si s'haguessin inclòs els pacients que van respondre al placebo (Perez et al., 2001). Es va arribar a la conclusió que els resultats haurien estat els mateixos i també s'hauria observat un efecte positiu del pindolol respecte el placebo en el tractament de la depressió major. Donats aquests càlculs, es va decidir quan es va dissenyar aquest nou estudi que no calia fer una fase inicial amb placebo.

En canvi, en l'estudi del DU125530 vs placebo i fluoxetina es va decidir un disseny amb una fase inicial de placebo perquè no es coneixia quin efecte podia tenir aquesta molècula en el tractament de la depressió. No hi havia cap assaig clínic realitzat fins el moment. Es va seguir el mateix disseny que per l'estudi del pindolol realitzat anteriorment pel nostre grup. Una fase inicial de placebo amb simple cec i posteriorment aleatorització a dues branques de tractament i doble cec. En l'estudi del DU125530, 7 pacients van respondre a placebo. La proporció de pacients que van respondre a placebo en el present estudi (14%) és similar a l'anterior estudi realitzat pel nostre grup el 1997 amb pindolol (14,45%) (Perez et al., 1997). Aquestes dades fan pensar que la mostra de pacients depressius era força homogènia en els diversos estudis realitzats.

Mida de la mostra

En ambdós estudis es va aturar el reclutament previst a la meitat de la mostra, en l'estudi de pindolol la mostra prevista era de 60 i es va aturar quan la N era de 30 i l'estudi del DU125530 la mostra prevista era de 100 i es va aturar quan la N era de 50.

En l'estudi de pindolol vs placebo i citalopram pel tractament de la depressió es va aturar al observar-se ja un efecte positiu en l'anàlisi intermedi. Es va pensar que augmentar la mostra no modificaria els resultats. Es va realitzar un anàlisi únicament dels pacients que responien per determinar si el resultat observat era atribuït a la diferència entre rebre pindolol o placebo i es van confirmar els resultats a favor del pindolol. Per tant el fet d'excloure la fase de placebo no penso que hagi tingut una influència significativa en els resultats de l'estudi.

Per altra banda, en l'estudi del DU125530 vs placebo i fluoxetina es va aturar la mostra quan s'havien reclutat 50 pacients i es va fer un anàlisi intermedi. Els resultats eren negatius i es va calcular, en relació a l'efecte observat, que encara que augmentéssim la mostra no n'observaríem cap diferència. Per tant es va decidir aturar l'estudi ja que no oferíem cap benefici als pacients.
Tot i això no es podria descartar que si s'hagués augmentat la mostra potser s'hagués arribat a observar algun tipus d'efecte i aquesta és una limitació de l'estudi.
Fins aquí les possibles explicacions per les discrepàncies observades. A continuació es discuteixen altres aspectes rellevants.

11) Us clínic del pindolol

El pindolol sembla una estratègia útil en el tractament de la depressió, tant per escurçar-ne el temps de latència com per millorar-ne l'eficàcia sobretot en aquells pacients que no presenten resistència als antidepressius. Actualment però, a nivell de pràctica clínica habitual, hi ha dificultats en utilitzar-lo ja que no es troba disponible en el mercat espanyol.
La dosi que nosaltres hem utilitzat, 15 mg/dia, és una dosi amb possible efecte hipotensor, ja que el pindolol s'utilitza a dosis de 5-30 mg/dia com a β-bloquejant. En el nostre estudi només es va detectar diferències en la freqüència cardíaca al final de l'estudi. Tot i la significació estadística va ser una troballa sense cap repercussió clínica. La tensió arterial, que era mesurada amb el pacient dret i en decúbit, no es va veure modificada. El pindolol, es mostra doncs com un fàrmac segur a nivell cardiològic i només caldria tenir en compte el risc hipotensor en pacients amb patologia cardíaca. Una possible limitació a nivell clínic del pindolol seria en pacients amb patologia bronquial o asmàtica degut al seu efecte β-bloquejant.
El pindolol ha mostrat eficàcia per escurçar el període de latència dels antidepressius i augmentar-ne la resposta en pacients que presenten depressions amb poca resistència farmacològica i també en pacients amb un primer episodi depressiu (Geretsegger et al., 2008, Portella et al., 2009). Aquest grup de pacients és molt nombrós tenint en compte l'alta prevalença de la depressió i solen ser atesos a nivell d'atenció primària o en el primer nivell assistencial psiquiàtric. Per tant l'ús del pindolol en aquests pacients podria millorar molt l'evolució i el pronòstic i probablement evitar cronicitat.
El pindolol també ha estat provat en diverses mostres de pacients ingressats, amb símptomes psicòtics i com a adjuvant a la teràpia electroconvulsiva amb resultats positius (Zanardi et al., 1998, Shiah et al., 2000), o sigui que també ha resultat eficaç en el tractament de quadres depressius greus.

Una possible limitació de l'estratègia de potenciació amb el pindolol a nivell clínic, és la necessitat de realitzar un tractament amb diversos medicaments (3 comprimits/dia de pindolol i 1 comprimit/dia d'antidepressiu). El pacient depressiu habitualment ja compleix poc amb el tractament prescrit (Oller-Canet et al., 2011) (veure article a l'annex). Un pobre compliment terapèutic disminuiria l'eficàcia del tractament adjuvant amb pindolol i això en limitaria el seu ús a nivell clínic. També es pot pensar que el tractament combinat amb múltiples fàrmacs pot dificultar el maneig de la depressió a l'atenció primària. Però els metges de família, estan acostumats a tractar pacients complexes, sovint polimedicats i solen utilitzar també altres medicacions adjuvants quan tracten una depressió, com per exemple benzodiazepines o hipnòtics.

Existeixen també els estudis de fàrmaco-economia en què es valora el cost-eficàcia de l'estratègia de potenciació del pindolol i aquests troben un descens dels costos en els pacients tractats amb pindolol respecte el placebo. Aquest descens és principalment degut a un descens dels costos mèdics (principalment menys ingressos psiquiàtrics) com s'ha observat en l'anàlisi de dos dels assajos clínics realitzats anteriorment (Tome and Isaac, 1998a, Sacristan et al., 2000). Per tant la potenciació del tractament amb pindolol semblaria ser una estratègia que disminuiria els costos mèdics per la malaltia depressiva.

Per tant a nivell de pràctica clínica els pacients que es podrien beneficiar de la potenciació amb pindolol serien aquells pacients amb depressió major amb poca resistència farmacològica i primers episodis depressius. Com que ha resultat d'utilitat en pacients greus, seria d'utilitat tant en atenció primària com per a tractament de pacients deprimits que per la seva gravetat són derivats a l'especialista o que requereixen ingrés hospitalari.

12) Limitacions

Existeixen diverses limitacions dels estudis que configuren aquest treball de tesi que s'ha anat desenvolupant en els anteriors apartats:

No es disposen de nivells plasmàtics de pindolol, DU125530 ni tampoc de neuroimatge. Si es disposés d'aquesta informació es podria establir amb més fiabilitat la relació establerta en la hipòtesi de la tesi, que el bloqueig del receptor 5-HT1A i la seva dessensibilització és el responsable de l'escurçament de la latència de la resposta antidepressiva dels ISRS.

En l'estudi del pindolol no es va realitzar període de placebo inicial i en canvi en el del DU125530 sí es va realitzar. Tot i que els càlculs basats en els estudis previs de pindolol descarten que els pacients que responen a placebo tinguin una influència en el resultat (Perez et al., 2001), la mostra de pindolol és petita i podria constituir una limitació de l'estudi.

La resistència als antidepressius sembla ser un factor de no resposta a l'estratègia de potenciació del pindolol. En els nostres estudis no es van incloure pacients amb resistència prèvia als antidepressius, tot i que hi havia una proporció elevada de pacients que presentaven depressió recurrent (40% en l'estudi de pindolol i 50% en l'estudi de DU125530). La proporció de pacients que presentaven un episodi depressiu que durava més de 6 mesos en el moment d'incloure'ls als estudis era del 10% en l'estudi de pindolol i del 40% en l'estudi del DU125530. Per tant la presencia en els pacients de factors associats a resistència al tractament antidepressiu podria haver enterbolit l'avaluació dels resultats.

No es va realitzar una avaluació dels pacients en el seguiment posterior a l'estudi clínic. La majoria van continuar essent atesos però no tenim dades dels que van continuar presentant resistència al tractament ni les seves característiques i aquest informació potser ens hauria ajudat a aclarir la tipologia de pacients que es beneficiaria més de l'estratègia del pindolol.

Per altra banda els pacients van ser reclutats d'atenció primària, consultes externes de psiquiatria i urgències de psiquiatria. Podria ser que els pacients fossin menys greus i la resposta al placebo fos més important. Però és poc probable, ja que els criteris d'inclusió en quant a gravetat clínica (puntuació de la HDRS) eren els mateixos que s'utilitzen en la majoria d'estudis sobre tractament antidepressiu.

Altres limitacions d'aquesta tesi són les pròpies de la recerca en psiquiatria. Per una part el fenotip del trastorn depressiu major inclou sovint un quadre heterogeni de pacients que dificulten la conclusió de resultats generalitzables. També la recerca en psiquiatria assumeix com a vàlids els models de depressió en recerca animal que no poden incloure l'essència més "humana" de la depressió. Per altra banda els models experimentals solen estudiar regions concretes i paràmetres concrets biològics, sovint forçant les condicions ambientals i es desconeix si aquests fenòmens es donen realment en el cervell de les persones.

13) Paper del receptor 5-HT1A implicacions pel futur del tractament antidepressiu i vies futures de recerca

Els estudis presentats en aquesta tesi aporten més evidència de la implicació del receptor 5-HT1A en la latència de resposta dels antidepressius monoaminèrgics. El bloqueig del receptor 5-HT1A a nivell presinàptic o bé la dessensibilització del receptor amb agonistes parcials aconsegueix disminuir l'efecte d'autoregulació i interferir en els mecanismes homeostàtics que té la neurona serotoninèrgica i escurçar i augmentar la resposta als ISRS. Aquest efecte però queda anul·lat pel bloqueig del receptor postsinàptic 5-HT1A, situat a nivell córtico-límbic. Per tant les estratègies futures passarien per desenvolupar un bloqueig del receptor 5-HT1A presinàptic de manera selectiva. Per tant tots aquells fàrmacs que siguin capaços d'aportar un

augment de la transmissió serotoninèrgica a nivell cortical i bloquejar/dessensibilitzar de manera selectiva els receptors 5-HT1A presinàptics tenen una via important de desenvolupament. El desenvolupament de la vortioxetina amb una acció sobre diferents receptors serotoninèrgics i que presenta una bona eficàcia clínica pot ser una via per continuar desenvolupant fàrmacs antidepressius.

Per altra banda hi ha una dificultat clara a l'hora de d'actuar de manera selectiva sobre els receptors 5-HT1A presinàptics, donada la manca de selectivitat dels diversos fàrmacs amb afinitat pel receptor, com la vilazodona i la vortioxetina. Ambdós fàrmacs presenten també una acció a nivell postsinàptic que podria interferir en l'acció antidepressiva.

Recentment s'ha desenvolupat l'ús de *si*RNA i ofereix una possibilitat terapèutica molt interessant. Les sondes de RNA que utilitzen un ISRS com a vehicle, aconsegueixen anar directament al rafe on bloquegen l'expressió del receptor 5-HT1A presinàptic de manera selectiva, sense arribar a modificar el 1A postsinàptic (Bortolozzi et al., 2012a).

Aquesta estratègia juntament a l'acció combinada sobre altres receptors serotoninèrgics podria ser una manera de millorar l'eficàcia dels antidepressius que actuen a través del sistema monoaminèrgic.

12. Conclusions

1. El receptor serotoninèrgic 5-HT1A té papers diferents en funció de la seva **localització** en relació al tractament antidepressiu. Quan es dona un ISRS a nivell **presinàptic** (al rafe) la seva dessensibilització és necessària perquè es produeixi un augment de serotonina a nivell cortical i està implicat en la latència de resposta dels antidepressius. Per altra banda el receptor 5-HT1A en localització **postsinàptica** (cortical) és necessària la seva activació perquè es produeixi l'acció antidepressiva.

2. El pindolol, fàrmac **antagonista parcial** del receptor 5-HT1A, **accelera i augmenta** la resposta al tractament antidepressiu. El DU125530, **antagonista complet** del receptor 5-HT1A no accelera ni augmenta la resposta antidepressiva.

3. El pindolol presenta una major **afinitat** pels receptors 5-HT1A presinàptics que pels 5-HT1A postsinàptics. El DU125530 presenta igual afinitat pels receptors presinàptics que pels receptors postsinàptics 5-HT1A. Aquesta diferent afinitat pot explicar en part les diferències observades a nivell clínic entre el pindolol i el DU125530.

4. El **bloqueig complet del receptor 5-HT1A postsinàptic** generat pel DU125530 anul·la l'efecte beneficiós que s'observa amb el pindolol. L'augment de serotonina a nivell cortical que s'observa en els estudis preclínics resultant del bloqueig del receptor 5-HT1A al rafe, queda anul·lat pel bloqueig del receptor 5-HT1A a nivell postsinàptic (cortical).

5. El pindolol és poc eficaç en pacients amb **resistència** al tractament antidepressiu. La resistència al tractament antidepressiu sembla un factor limitant a l'estratègia de potenciació del tractament amb pindolol.

6. El pindolol **accelera i augmenta** la resposta antidepressiva sobretot en pacients deprimits no resistents al tractament.

7. Altres **variables clíniques** com la gravetat, la durada de l'episodi o la presència de malenconia no semblen influir en la resposta al pindolol. Sembla ser que en primers episodis depressius la resposta al pindolol podria ser millor.

8. **Dosis** més altes de pindolol (15 mg/dia) són eficaces per la potenciació del tractament antidepressiu, d'acord amb resultats previs de la neuroimatge que indicaven una ocupació del receptor 5-HT1A presinàptic baixa amb les dosis habituals (7,5 mg/dia)

9. L'acció **β-blocant** del pindolol no sembla tenir rellevància en la resposta del pindolol

10. Els **nivells plasmàtics dels antidepressius** utilitzats en els nostres estudis no tenen relació amb la resposta antidepressiva, d'acord amb treballs previs que tampoc detecten relació entre nivells plasmàtics i resposta antidepressiva.

11. Els **nivells plasmàtics de pindolol** no semblen tenir relació amb al resposta antidepressiva

12. L'ús del **citalopram endovenós** pot ser una estratègia útil pel tractament de la depressió. Tenir nivells plasmàtics alts d'inici podria ser una estratègia que desbordés els mecanismes d'autoregulació de la neurona serotoninèrgica mediats pel receptor 5-HT1A presinàptic i millorar la resposta antidepressiva.

13. El pindolol és un fàrmac **útil** en el tractament de la depressió. Si estigués disponible al nostre mercat seria una estratègia a tenir en compte a l'hora de tractar pacients amb depressió no resistents.

14. El **futur** de l'estratègia amb els fàrmacs que actuen millorant la transmissió serotoninèrgica passaria pel desenvolupament de molècules que tinguin selectivitat pels receptors 5-HT1A a nivell del rafe. D'aquesta manera s'interferiria en els mecanisme d'autoregulació de la neurona serotoninèrgica sense alterar la transmissió del receptor 5-HT1A postsinàptic en localització cortical.

Annex

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Do depressed patients comply with treatments prescribed? A cross-sectional study of adherence to the antidepressant treatment

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Introduction. Compliance with antidepressant treatment is a very relevant factor in the outcome of depressive disorders. Poor compliance has been associated with worse outcome, increased rate of relapses and greater cost. This study has aimed to describe adherence to antidepressant treatment in a sample of primary care patients with a diagnosis of depression in 2007.

Methods. Randomized sampling was made of patients with depression and antidepressant treatment attended in two primary care teams. Their medical records were reviewed to obtain the total number of prescriptions given to patients and the total number of prescriptions dispensed in the pharmacies. The difference between prescriptions written and collected was calculated. A difference of ± 2 was considered as good compliance. Results are shown as percentages. Comparisons were made with the chi-square, Student's T and ANOVA tests, where appropriate.

Results. The simple was made up of 212 patients. Mean age was 63.2 years (SD 15.27). In the sample, 66.5% were treated with only one antidepressant and 24.1% with two. The percentage of non-compliance was 33.96% (95% CI: 25.35–40.57). Treatment-adherent patients have a lower percentage of long-term treatment with other drugs. The percentage of treatment-adherent women was higher than non-adherent (p=0.015). No differences were found in compliance among patients treated in the mental health center.

Conclusions. One third of patients on antidepressant drug treatment were non-compliers because the drugs were not picked up properly from the pharmacies. We need to develop strategies to improve the therapeutic adherence of patients.

Key Words:
Depressive disorder, Antidepressant treatment, Compliance, Descriptive study

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¿Toman los pacientes deprimidos el tratamiento prescrito? Estudio descriptivo sobre el cumplimiento del tratamiento antidepresivo

Introducción. El cumplimiento del tratamiento antidepresivo es un aspecto importante en la evolución de los trastornos depresivos. El mal cumplimiento se ha asociado a una peor evolución, a un mayor número de recaídas y mayor coste económico. El objetivo de este estudio es describir el cumplimiento del tratamiento antidepresivo en una muestra de pacientes de atención primaria (AP) con diagnóstico de depresión durante el año 2007.

Método. Se realizó un muestreo aleatorio de pacientes con diagnóstico de depresión y tratamiento con antidepresivos atendidos en dos equipos de (AP) y se revisaron las historias clínicas. En ellas consta el número de recetas prescritas y el número de recetas recogidas en la farmacia. Se calculó la diferencia entre recetas prescritas y recogidas. Una diferencia de ± 2 se consideró un buen cumplimiento. Se mostraron los resultados en porcentajes y se realizaron comparaciones Ji cuadrado, t-student y ANOVA cuando procedía.

Resultados. La muestra estaba compuesta de 212 pacientes. La edad media era de 63,2 años (DE =15,27). El 66,5% estaba en tratamiento con un antidepresivo y el 24,1% con dos. El porcentaje de pacientes no cumplidores era del 33,96% [IC 95% (27,35-40,57)]. Los pacientes cumplidores presentaban un menor porcentaje de tratamiento con otros fármacos crónicos. En los cumplidores el porcentaje de mujeres era superior que en el de no cumplidores (p = 0,015). No había diferencias en el cumplimiento en los pacientes atendidos en el centro de salud mental.

Conclusiones. Un tercio de los pacientes en tratamiento farmacológico antidepresivo no eran cumplidores puesto que no lo retiraban de forma adecuada de las farmacias. Es necesario desarrollar estrategias de mejora de la adherencia terapéutica de los pacientes.

Palabras clave:
Trastorno depresivo, Tratamiento antidepresivo, Cumplimiento, Estudio descriptivo

INTRODUCTION

Major depression is a frequent disease having a very significant psychosocial impact. In the ESEMeD epidemiological study carried out in Spain,[1] a life-long prevalence of depression was calculated to be 10.6%, and at one year 4%. It affects almost twice the number of women as men, with 14.4% prevalence in women and 4.3% in men.[2] In the primary care clinics of Catalonia, 20% of the patients seen had a major depressive disorder or dysthymic disorder.[3] The World Health Organization (WHO) calculated the impact of depression in 2008, determining that it was the first cause of loss of years of health due to disease in the world.[4] Patients with depression tend to take less care of their health[5] and comply three times less with the medical recommendations in comparison to non-depressed patients.[6]

Recurrence rates of depression have been calculated to be at least 50% after a first major depression episode and 80-90% if the patient has had two or more depressive episodes.[7, 8] Evidence in favor of maintenance treatment to prevent relapses has been increasing in recent years with the appearance of several meta-analysis confirming its efficacy, [9, 10] independently of the patient's age or severity of the depressive episode.[11, 12] These are the reasons why most of the treatment guidelines for major depressive disorder recommend carrying out treatment for six months after a major depressive episode and up to 2 years if the recurrence rate is elevated.[13, 14] Treatment noncompliance would represent an important obstacle to maintain remission of the symptoms. Lack of antidepressant treatment adherence has been associated to a decrease in efficacy and increase in the persistence of depressive symptoms[15, 16] as well as an increase in cost in the treatment and indirect costs.[17]

Lack of adherence may increase disease recurrence[15, 16, 18] and is an obstacle to transfer the efficacy obtained in clinical trials to the common practice.[19, 20] The research performed in this area of interest has serious problems such as the definition itself of the term and the methods to measure it. Adherence would include two concepts: adherence to the dose and form of administration and persistence in the duration of the treatment prescribed.[20, 21] In regards to the procedure used to evaluate adherence, there are subjective and objective methods.[22] The subjective methods are self-reports or interviews of the patients, the clinical opinion of the professional attending to them.[20, 21] The objective methods include, for example, counting the pills in the container, monitoring serum levels of the drug, electronic dispensation systems or databases of pharmacies.[20, 22]

The literature on antidepressant treatment adherence provides unequal results based on the instruments used to measure it in the population studied. Antidepressant treatment noncompliance varies from 10 to 60%[23, 24] and has not significantly changed with the introduction of new antidepressants. The most potent predictive factors are not related with clinical or sociodemographic variables but rather with the attitudes of the patient towards the disease and the treatment, as well as their system of beliefs on health.[19, 20, 22] Socioeconomic status and gender seem to influence treatment adherence, this being greater in women and in persons with higher educational and economical level.[24, 25, 26] In addition, it has been hypothesized that the prescription of multiple drugs may make treatment compliance more difficult.[27] A study in which therapeutic compliance was evaluated with a questionnaire seemed to indicate that it is worse in those patients who receive other treatment for organic diseases.[26]

The objective of this study has been to estimate antidepressant treatment adherence indirectly, by counting of prescriptions withdrawn in the pharmacy, in patients with diagnoses of depression and attended by two primary care teams, and to analyze its relationship with the presence of other chronic conditions and other long-term treatments. The hypothesis of the study has been that worse treatment compliance would be found in those patients with more long-term drug treatments.

METHODOLOGY

A descriptive, cross-sectional study of retrospective data performed by two primary care teams (PCT) was conducted. The teams were Encants and Camp de l'Arpa, located in the city of Barcelona. The study subjects were the population assigned to the two PCTs (45,000 assigned patients) over 17 years of age who had the following diagnoses recorded in the computerized clinical record: diagnosis of depression (F32 -depressive episodes; F33 -recurrent depressive disorder;

F34.1 -dysthymia; F41.2 -mixed anxious depressive disorder; F43 -adaptive disorder - of the ICD10) and who were receiving active antidepressant treatment during 2007. Those patients who had been transferred from the site or died during this period or who had been prescribed treatment for less than 3 months during 2007 were excluded from the study. In all, 1734 patients were included in the sample.

Patient screening was performed by simple randomization from the list of those who complied with the selection criteria. The sample size was calculated to detect a prevalence of 63% (median of compliance according to different measurement methods of adherence[24]), with an alpha error of 0.06 and 95% confidence level. The resulting sample was 212 patients.

The following variables were collected from the clinical record: gender, antidepressant drug (active ingredient, number of active ingredients, number of prescriptions prescribed during the year 2007, number of prescriptions dispensed in pharmacy during the year 2007), number of active long-term drugs prescribed (at least 3 months of prescription), prescription of anxiolytics in 2007 (yes /no), presence of chronic condition (arterial hypertension (AHT), ischemic heart disease, diabetes mellitus, chronic obstruction pulmonary disease (COPD), osteoporosis and dyslipidemia). The number of visits made to the PCT (family doctor and nurse) and to the reference mental health sites was also reviewed.

Drug compliance was determined through the information collected in the computerized clinical record (CCR) and prescription and dispensation. The CCR made it possible to access information on the dispensation of prescriptions in the pharmacy, monthly, and according to the drug specialty. The following formula was calculated: no. prescriptions prescribed - no. prescriptions dispensed in pharmacy, classifying them into complier when the patient had a difference of less than two prescriptions in absolute value and non-complier when the difference was greater. This difference was considered as valid when taking into account those prescriptions prescribed in the last two months of 2006 or dispensed in the first two months of 2008. Considering that the mean prescription is one prescription per month as the antidepressant treatment containers usually have 28 tablets and that the long-term medication prescriptions are administered every two months, a margin of two prescriptions was accepted to consider a patient as complier. The percentage of drug compliance was analyzed with its 95% confidence interval, globally and by groups of active ingredients. The relationship between being a complier and the rest of the variables was compared using the Chi Square and Students' T test or Mann-Whitney test, depending on the normality of the quantitative variables. A multivariate logistic regression analysis whose dependent variable was antidepressant treatment compliance (yes/no) was carried out. Independent variables included age, gender and the clinical variables that were significant in the bivariate analysis.

Table 1 Demographic and clinical characteristics of the patients

	Frequency (N=212)	%
Women	162	76.4
Under 65 years	112	52.8
Therapeutic groups		
SSRI	181	85.4
Duals (duloxetine/venlafaxine)	30	14.15
Tricyclics	18	8.5
Mirtazapine/mianserin	14	6.6
Others	14	6.6
Chronic condition recorded	143	67.5
Under treatment with other long-term drugs	179	84.4
They take anxiolytics	150	71.1
Seen in mental health Center	37	17.5

Table 2 Diagnostic distribution of depressive disorders. Some patients had more than one diagnoses

	N	%
F32. Depressive episodes	185	80
F33 Recurrent depressive episodes	17	7.4
F34.1 Dysthymia	7	3
F41.2 Mixed anxious depressive disorder	18	7.8
F43 Reactions to serious stress and adjustment disorders	4	1.7

RESULTS

The 212 patients included in the study came from two primary care teams in Barcelona. Mean age was 63.2 years (SD=15.27). Demographic and clinical characteristics are described in Table 1. All the patients had been diagnosed of depressive disorder (see table 2 for distribution of diagnoses). A total of 66.5 % were under treatment with a single antidepressant 24.1% with two antidepressants and 8.1% with three or more antidepressants. The antidepressants used most were selective serotonin reuptake inhibitors (SSRI) (table 2). During the treatment, 71.1% of the subjects took anxiolytics (benzodiazepines or hypnotics) as treatment concomitant to the antidepressants (the duration of the anxiolytic treatment was not evaluated). The percentage of

patients with chronic condition recorded was: 50.5% hypertension, 38.7% dyslipidemia, 11.8% diabetes, 6.1% osteoporosis, 5.2 % chronic obstructive pulmonary disease and 2.4% ischemic heart disease. A total of 68.5% of the patients had one or more chronic conditions and 84.4 % of the patients were receiving long-term treatment with one or more drugs. The patients were attended by primary care teams with a mean of 11.48 visits per years (SD =10.6) and 50% of the patients made 9 or more visits. Follow-up was made by 17.5% of the patients in the mental health center and the rest were attended by the primary care team. The patients who were seen in the mental health made a mean of 5.47 visits/year (SD =7.20) and 50% had 3 or more visits. The percentage of non-adherent patients was 34% [95% CI (27.3-40.5)]. The non-compliers had a higher percentage of long-term drug treatment (p=0.013). No relationship was found between compliers and the rest of the variables studied (table 3). The multivariate analysis confirmed that having a prescription of any other long-term treatment increases the likelihood of being a poor complier of the antidepressant treatment, independently of age and gender of the patient (OR: 3.35; 95% CI: 1.18- 9.54). No differences in compliance were found according to the type of antidepressant prescribed or if concomitant treatment with anxiolytics was received. There was also no relationship between compliance and the rest of the variables studied. The compliance rates were analyzed in the SSRI-treated group of patients (see table 4). Among the complier patients, 82.2% were women versus 65.4% among the non-complier's (p=0.015). In this group, the non-compliers also had a higher percentage of treatment with other long-term prescription drugs (p=0.006). When the variables were adjusted among themselves with the multivariate analysis, the relationship between being a male and having lower compliance was confirmed (OR: 2.39; 95% CI: 1.12- 5.09) and having at least one long-term drug prescribed and being a poor complier (OR: 6.28; 95% CI: 1.37- 28.85).

Table 3 Comparison between complier and non-complier patients

	Cumplidores (total=140)	No cumplidores (total=72)	p
Gender			
Women	78.6%	72.2%	0.302
Men	21.4%	27.8%	
Age (years)			
Under 65	54.3%	50.0%	0.554
65 and over	45.7%	50.0%	
Chronic disease recorded			
None	35.0%	27.8%	0.228
One or more	65.0%	72.2%	
Long-term treatment with other drugs			
No	20.0%	6.9%	**0.013**
Yes	80.0%	93.1%	
They take anxiolytics			
No	27.1%	32.4%	0.427
Yes	72.9%	67.6%	
Seen in mental health center			
No	85.0%	77.8%	0.190
Yes	15.0%	22.2%	

DISCUSSION

There are a variety of methods that make it possible to analyze the grade of compliance.[21] The method used in this study is based on the registry of prescriptions dispensed to patients in the pharmacy. This registry is reliable, and has easy and rapid access from the management program of the e-CAP (primary health care team) clinical record in the usual clinical practice in the consultation. This is a novel indirect, objective measurement method[28] with null possibility of manipulation by the patient. It is easy and clear for the professional to interpret, the questions all being differential regarding the other measurement methods of compliance. On the other hand, it is not possible to assure that the medication withdrawn from the pharmacy was finally administered, this fact being the principal limitation of the method. It is also not possible to take into account the drugs withdrawn and pharmacies outside of Catalonia, as they do not share the same prescription registry computer system. In this study, complier is considered to be that patient who withdrew 100% of the drugs prescribed from the pharmacy during the year, accepting a variation of ± 2 prescriptions due to the measurement method.

In this study, one third of the patients were classified as non-compliers. This is slightly lower than in other studies that have evaluated antidepressant treatment compliance with other methods, although the results have been very variable and have varied from 10 to 60% .[23, 29, 30] It is very likely that compliance has been overestimated because it has not been possible to assure that the medication was taken once withdrawn from the pharmacy. There are many direct and indirect methods to measure compliance, but most of them are difficult to apply in the daily clinical practice. This novel method, in spite of its limitations, offers true, reliable information and rapid access from the patient clinic. In spite of these limitations, according to the existing literature, this method has been shown to be valid to analyze treatment adherence, given that it evaluates the grade of compliance similarly to other methods and is adequately related with the clinical results.[31]

Treatment compliance in this study seems to also be slightly superior to other chronic medical diseases that vary

Table 4 Comparación entre pacientes cumplidores y no cumplidores, en los que tomaban ISRS

	Compliers (total=129)	Non- Compliers (total=52)	p
Gender			
Women	82.2%	65.4%	0.015
Men	17.8%	34.6%	
Age (years)			
Under 65	53.5%	48.1%	0.510
65 and over	46.5%	51.9%	
Chronic disease recorded			
None	32.6%	30.8%	0.862
One or more	67.4%	69.2%	
Long-term treatment with other drugs			
No	20.2%	3.8%	**0.006**
Yes	79.8%	96.2%	
They take anxiolytics			
No	29.7%	25.0%	0.527
Yes	70.3%	75.0%	
Seen in mental health center			
No	87.6%	80.8%	0.236
Yes	12.4%	19.2%	

from 30 to 50%.[32, 33, 34] Many studies have tried to determine the causes of low compliance in patients with depression. One of the factors postulated as being a determining factor when improving compliance is the profile of drug side effects.[35] In this study, better treatment compliance has not been found with SSRIs regarding treatment with other antidepressants, possibly due to the limited number of patients being treated with other antidepressants (tricyclics, etc.) that have not made it possible to find differences.

As was to be expected, no differences were found in regards to drug compliance among the different SSRIs, as well as in patients who received concomitant and selective treatment. Multiple drug treatment with other long-term drugs has been found to be a factor determining adherence, it being the only clinical factor related with compliance in this study. These results agree with other studies published.[27, 36] The number of daily dosages of antidepressant drugs taken was not analyzed, a question that has been demonstrated to be important when improving compliance,[37] although most of the SSRIs are administered as a single daily dose.

It also was not possible to observe any difference in regards to compliance among patients who received follow-up by Primary Care or by the Mental Health Center, on the contrary to other studies.[29] On the other hand, adherence was similar, regardless of the number of visits made to the MHC, so that we observed that a more frequent follow-up does not ensure better compliance nor does low compliance seem to generate more visits.

One of the limitations of our study is the fact that the patients were classified into two categories, without considering the different grades of compliance. This facilitated the interpretation of the results, but did not make it possible to differentiate between patients who had not withdrawn any prescription from those who had withdrawn 75%. On the other hand, no analysis was made regarding at what point of the treatment the abandonment or noncompliance occurred, nor the severity of the depression. When collecting data of patients with at least three months of treatment, early dropouts were ruled out.

The results of this study show that multiple drug treatment is a factor influencing antidepressant treatment adherence and primary care, similar to other studies.[26] Multiple drug treatment is common in elderly patients as occurs in this sample (mean age 63 years). This indicates the need to develop strategies that improve antidepressant treatment compliance, especially in this population segment in order to improve the clinical course of these patients.

For this reason, it is necessary to intensify certain strategies aimed at improving compliance in both primary care and specialized care, these strategies being education to the patient on their disease, informing on the most frequent adverse effects on which tolerance will be developed, involving the caregivers and family, above all in elderly patients, using calendars, use of dose reminders for the pills, and other strategies that have demonstrated efficacy in some studies.[38, 39]

CONCLUSIONS

One third of the patients receiving antidepressant treatment do not adequately comply with the drug treatment, according to the accountability of the drugs withdrawn in the pharmacy. Strategies must be developed to improve drug treatment compliance, especially in the population with multiple drug treatment.

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