

[ORIGINAL ARTICLE]

A Systematic Review of the Effectiveness of Antianxiety and Antidepressive Agents for Functional Dyspepsia

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Abstract:

Objective Functional dyspepsia (FD) is defined as persistent or recurrent pain or discomfort centered in the upper abdomen without organic disease. Psychosocial factors have been proposed as an important element in the pathophysiology of FD. Therefore, psychotropic agents having antianxiety or antidepressive action are expected to alleviate FD. We previously reported on the treatment of FD using such agents in a systematic review, wherein the effectiveness of the agents on FD was suggested, although there were several limitations. We searched for articles on this subject after our systematic review and re-reviewed them systematically.

Methods Articles were searched for in MEDLINE from 2003 to 2014 using terms related to antianxiety or antidepressive agents. Clinical studies in which the effectiveness of such agents was clearly stated were selected from the retrieved articles. The newly selected and previously selected studies were combined, and statistical analyses were carried out.

Results Nine studies were selected. Five of the studies indicated a significant symptomatic improvement using psychotropic drugs. A statistical analysis suggested a significant treatment effect of psychotropic agents having antianxiety or antidepressive action [pooled relative risk (PRR), 0.72; 95% confidence interval (95% CI), 0.52-0.99; $p=0.0406$] but did not show a significant benefit of treatment with agents having an antidepressive action alone (PRR, 0.63; 95% CI, 0.38-1.03; $p=0.0665$).

Conclusion Our systematic review suggested that psychotropic drugs having antianxiety and antidepressive actions as a whole might be effective in alleviating FD symptoms, whereas those having only antidepressive action were not effective.

Key words: functional dyspepsia, psychotropic agents

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Introduction

Functional dyspepsia (FD) is defined as persistent or recurrent pain or discomfort centered in the upper abdomen, without organic disease. FD is common in the general population, and the prevalence of FD has been reported to range from 11% to 17% in Japan (1, 2). Multiple factors are associated with the development of FD (3). Psychological stress sometimes exacerbates dyspeptic symptoms in healthy vol-

unteers (4) and FD patients (3), and patients with physical complaints in a depressive or anxious state tend to describe their symptoms as being more severe than patients with physical complaints who are not in a depressive or anxious state (5). Psychosocial factors have been proposed as an important element in the pathophysiology of FD (3). Therefore, psychotropic agents having antianxiety or antidepressive action are expected to alleviate FD symptoms.

We previously published a systematic review of the treatment of FD with antianxiety or antidepressive agents in

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2005 (6). That review showed the effectiveness of psychotropic agents for the treatment of FD, and the authors recommended the use of these agents for the treatment of FD. However, as the available number of studies in that review was small and/or the studies were of poor quality, further clinical studies were needed to verify the effectiveness of FD treatment with psychotropic agents. We searched for clinical studies of psychotropic agents with antianxiety or antidepressive action for FD after our systematic review and reviewed the studies systematically. We added the newly searched studies to the studies from our previous review and re-analyzed all of the studies.

Materials and Methods

Literature search

We retrieved articles by searching the MEDLINE database limited to English-language, peer-reviewed articles on humans from 2003 to 2014 using the following keywords: functional dyspepsia AND [“antidepressant(s) OR antidepressant drug(s) OR antidepressive drug(s) OR antidepressive agent(s)” OR “antianxiety drug(s) OR antianxiety agent(s) OR anxiolytic drug(s) OR (minor) tranquilizer”]. We also examined the reference lists of published papers, such as reviews, to search for more articles.

Study selection

The inclusion criteria for selection were studies that reported whether or not symptoms of FD were improved by antianxiety or antidepressive agents, studies that pertained to the adult population, and studies that were the most informative when plural studies were published with the same content.

Data extraction

The following data were extracted from the selected studies: the number of recruited patients, background characteristics of the recruited patient population (age, sex, disease, mental state), study design, treatment dose and duration, the number of patients who received the allocated intervention, the effects of treatment based on the intention-to-treat principle or full analysis set, the symptoms that improved after treatment, and the number of subjects who dropped out because of side effects.

Statistical analyses

All statistical analyses were performed using the StatsDirect Version 3.0.150 software program (StatsDirect, Cheshire, UK). Regarding controlled studies in which the treatment efficacy was evaluated by comparing the percentage of patients with dyspeptic symptoms that improved or disappeared among a group receiving an actual agent with that in a group receiving a placebo, we assessed the effect of the agents by showing the pooled relative risk (PRR) with its 95% confidence interval (95% CI) and p value. The p values

less than 0.05 were considered statistically significant.

The PRR was calculated after adding the newly searched controlled studies to the four double-blind randomized studies (7-10) from our previous review (6). The PRR was calculated using the DerSimonian and Laird method. To quantify heterogeneity, I^2 was calculated. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity (11). The PRR was less than 1 when dyspepsia symptoms were improved by treatment with true drugs. A bias assessment plot was used to assess the publication bias and selection bias.

Results

We retrieved 80 articles by performing a computer search of the MEDLINE database from 2003 to 2014. Nine studies were ultimately selected according to the inclusion criteria (Table 1) (12-20). Seventy-one articles were excluded. Among them, 43 articles were review articles, including 1 systematic review, 5 articles did not pertain to the adult population, and 23 articles were not reports concerning the efficacy of psychotropic drugs with antianxiety or antidepressive action for FD (Fig. 1). No articles were newly selected from the reference lists of published papers.

In five of the nine studies, treatment with psychotropic drugs significantly improved dyspeptic symptoms. Significant improvement was reported in two of the four studies on drugs having antianxiety action (12-15) and in three of the five studies on drugs having antidepressive action (16-20). The recruited patients in two studies (16, 17) that showed that antidepressants were effective were patients who had not responded to acid-suppressive agents or prokinetic agents.

For the statistical quantitative analyses, three of the nine studies were selected (13, 19, 20), and six were excluded. The reasons why the six studies were excluded were as follows: four studies were not placebo-controlled (14, 15, 17, 18), and two studies did not include sufficient information about the number of patients who received the allocated intervention and the number who showed improvement (12, 16) (Fig. 1). A statistical analysis was done on a total of seven studies by adding these three studies to the four studies from our previous systematic review (7-10) (Table 2).

The numerical values necessary to calculate the PRR and 95% CI are shown in Table 2. The PRR was 0.72 (95% CI, 0.52-0.99; $p=0.0406$; Fig. 2). This result showed a significant benefit of the actual drugs over the placebo. The I^2 was 77.9% (95% CI, 44.4-87.7%), which showed that there was heterogeneity among the studies. The bias assessment plot (Fig. 3) exhibited asymmetry, which indicated both publication bias and selection bias.

Drugs with antidepressive action were used in five of the seven studies (Table 2). The PRR of the studies on these drugs was 0.63 (95% CI, 0.38-1.03; $p=0.0665$; Fig. 4). This showed that there was no significant benefit of the actual

Table 1. Clinical Studies Using Antianxiety or Antidepressive Agents for the Treatment of Functional Dyspepsia.

Studies (reference number)	The number of recruited patients	Male: Female	Mean age in years	The condition of recruited patients	Exclusion criteria for mental state	Study design	Treatment agent dose (duration)	The number of patients that received allocated intervention	ITT or FAS	Improved symptoms ^a	Side effects ^b
Antianxiety agents											
(12)	20	4:13	38.5	FD ^c	Excluding patients with current anxiety or depression	Double-blind randomized cross-over study	Buspiron 30mg (4 weeks) Placebo (4 weeks)	7	p<0.005*	post prandial fullness, early satiety, upper abdominal bloating	1
(13)	150	40:110	46.4	FD ^c	Excluding patients with anxiety or depression	Double-blind randomized controlled study	Tandospirone 30mg (4 weeks) Placebo	74 71	p=0.036*	upper abdominal pain and discomfort	1 0
(14)	79	29:50	52.9	FD ^c	No exclusion criteria for mental state	Randomized controlled study	Famotidine 40mg Mosapride 15mg Tandospirone 30mg	25 27 27	N/A***		0
(15)	64	N/A	N/A	FD ^c	No exclusion criteria for mental state	Randomized controlled study	Famotidine 40mg (8 weeks) Mosapride 15mg (8 weeks) Tandospirone 30mg (8 weeks)	23 21 20	NS****		0
Tricyclic antidepressive agents											
(16)	38	15:23	40.0	FD ^d who did not respond to PPI or prokinetic therapy	Excluding patients with depression	Double-blind randomized controlled study	Amitriptyline 12.5-50mg (8 weeks) Placebo	20 18	p=0.02*	nausea	4 0
(17)	27	N/A	N/A	FD ^e who did not respond to famotidine or mosapride therapy	Excluding patients with depression	Randomized controlled study	Amitriptyline 30mg (4 weeks) No medication (4 weeks)	14 13	p<0.01*	N/A	0 0
Levosulpiride											
(18)	140	34:106	N/A	FD ^e with dysmotility-like dyspepsia	No exclusion criteria for mental state	Randomized controlled study	Levosulpiride 75mg (8 weeks) Cisapride 30mg (8 weeks)	69 71	p=0.01** p=0.02**	Pain/discomfort, fullness, bloating, early satiety, nausea, and vomiting Pain/discomfort, fullness, bloating, early satiety, nausea, and vomiting	3 6
Serotonin reuptake inhibitors											
(19)	193	54:139	42.4	FD ^c	Excluding patients with a history of antidepressant use	Double-blind randomized controlled study	Sertraline 50mg (8 weeks) Placebo	98 95	NS*		14 8
Serotonin and norepinephrine reuptake inhibitor											
(20)	160	65:95	52.0	FD ^f	Excluding patients with a history of bipolar disorder or recent use of antidepressant	Double-blind randomized controlled study	Venlafaxine 75-150mg (8 weeks) Placebo	80 80	NS*		19 6

FD: functional dyspepsia, PPI: proton pump inhibitor, ITT: intention to treat, FAS: full analysis set, N/A: not available, NS: not significant.

a, Symptoms which improved significantly after treatment; b, The number of study subjects who dropped out because of side effects; c, FD based on ROME II criteria; d, FD based on ROME III criteria; e, FD based on ROME I criteria; f, Patients had persistent dyspeptic symptoms without any organic abnormality.

* Comparison of treatment effect by true drug and placebo. Significant improvement by a true drug was established when p<0.05.

** Comparison of pre- and post-treatment. Significant improvement after treatment was established when p<0.05.

*** Statistical analysis was not done for comparison of pre- and post-treatment by tandospirone. Famotidine was significantly superior to tandospirone (p<0.05).

**** Comparison of pre- and post-treatment by tandospirone. Famotidine was significantly superior to other drugs (p<0.05).

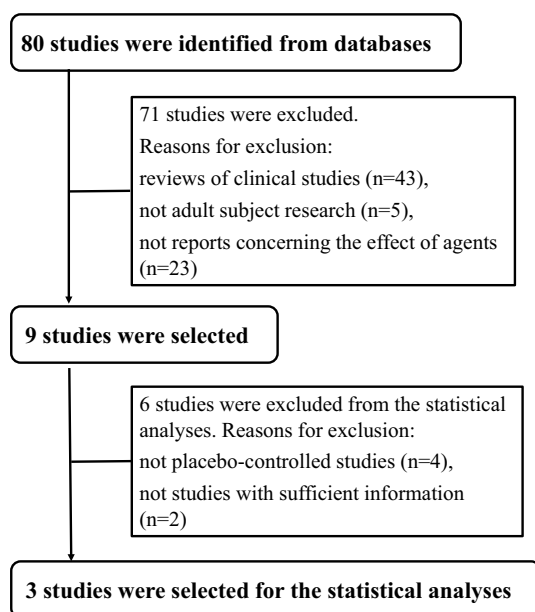


Figure 1. Flow chart illustrating the process of study selection.

drugs over the placebo. The I^2 was 82.9% (95% CI, 51.5-90.9%), which showed that there was heterogeneity among the studies.

More than 10% of patients treated with buspirone, amitriptyline, sertraline, or venlafaxine dropped out from the respective study protocols because of side effects. The symptoms of side effects were as follows: nausea and abdominal discomfort for buspirone; drowsiness and skin rash for amitriptyline; insomnia, constipation, and agitation for sertraline; and nausea, palpitations, sweating, sleeping disorders, dizziness, and visual impairment for venlafaxine. The study that showed the highest rate of protocol failure was the study on venlafaxine (20), and 19 of 80 patients who were treated with venlafaxine dropped out of the study.

Discussion

In the descriptive analysis of the current systematic review, the effectiveness of drugs having antianxiety action and antidepressive action in patients with FD was found in more than half of the studies examined. Furthermore, the results of the statistical quantitative analyses of the current review showed that the effectiveness of these drugs was the same as that in the previous systematic review (6). FD is a multifactorial disease with complex pathophysiology. The interaction of psychosocial factors and altered gut physiology via the brain-gut axis is known to be one of the pathophysiologies of FD (21). It has also been described that psychosocial factors contribute to symptoms of FD in the evidence-based clinical practice guidelines for FD published by the Japanese Society of Gastroenterology (JSGE) (3). The results of the current review showed that there is a subgroup of FD patients for whom psychotropic agents are effective. However, heterogeneity and publication or selection bias

persisted in the present review as in the previous one (6).

We examined two kinds of psychotropic agents: drugs having antianxiety action and drugs having antidepressive action. Regarding drugs having antianxiety action, only two placebo-controlled studies using chlordiazepoxide-clidinium bromide or tandospirone (7, 13) were included in the statistical analysis. Both studies showed that the actual drugs were superior to the placebo. Aside from these two studies, one placebo-controlled study using propantheline bromide in addition to diazepam (22) was included in the descriptive analysis of the former systematic review, and one placebo-controlled study using buspirone (12) was included in the current review. Propantheline bromide in addition to diazepam had a comparable effect to the placebo, while buspirone had a stronger effect than the placebo. Both tandospirone and buspirone are 5-hydroxytryptamine 1A (5-HT_{1A}) receptor agonists. 5-HT_{1A} receptor agonists may be effective for FD, although further clinical studies are necessary. Chlordiazepoxide-clidinium bromide, tandospirone, and buspirone are not simple anxiolytic drugs. Chlordiazepoxide-clidinium bromide allays anxiety and blocks cholinergic activity (7). Tandospirone and buspirone have an anxiolytic action that is not associated with benzodiazepines and are assumed to relax the proximal stomach (23, 24). Although benzodiazepine agents are often used as antianxiety agents, no studies investigated the effectiveness of a single use of benzodiazepine for FD in the previous or current reviews. Benzodiazepines are associated with increased risks of falls and hip fractures as well as vehicle crashes and induce tolerance and dependence (25). Therefore, when benzodiazepines are prescribed to FD patients, their potential benefits and risks should be carefully weighed.

Regarding drugs having antidepressive action, the current review did not show their effectiveness, although the effectiveness of these drugs was shown in the previous systematic review. The serotonin reuptake inhibitor (SSRI) sertraline and the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine were not superior to the placebo (19, 20). In the study with the SSRI fluoxetine, which was included in the previous review (6), the symptoms improved significantly after treatment (26). However, this study was an open study, and the symptoms improved in only the depressed FD patients. Although a recent meta-analysis of placebo-controlled studies of irritable bowel syndrome showed the effectiveness of SSRIs (27), there have been no studies on FD showing the effectiveness of SSRIs or SNRIs to date. Recently Talley et al. (28) conducted a randomized controlled trial to evaluate the effects of a tricyclic antidepressant and an SSRI on FD. Unfortunately, in this study, the effectiveness of the SSRI was not shown.

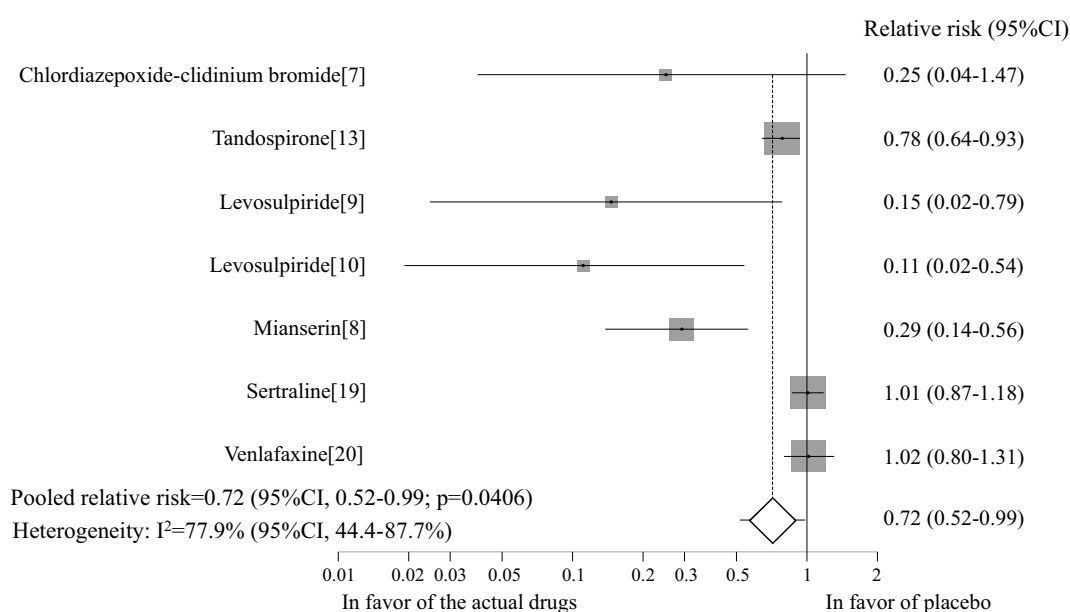
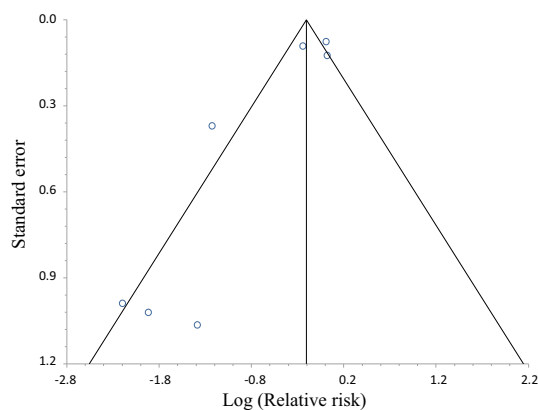
Furthermore, in the current review, 14% of the patients treated by sertraline and 24% of the patients treated by venlafaxine dropped out of their respective study because of side effects (19, 20). When an SSRI or SNRI is prescribed to FD patients, the merits and demerits should be carefully weighed. The beneficial effects of the tricyclic and tetracy-

Table 2. Studies for which Statistical Analyses were Done.

	The number of patients that received an actual drug		The number of patients that received a placebo	
	improved†	not-improved‡	improved†	not-improved‡
Antianxiety agents				
Chlordiazepoxide-clidinium bromide (7)	16	1	13	4
Tandospirone (13)	23	50	9	62
Antidepressive agents				
Levosulpiride (9)	16	1	9	6
Levosulpiride (10)	14	1	6	9
Mianserin (8)	19	6	4	18
Sertraline (19)	21	77	21	74
Venlafaxine (20)	30	50	31	49

† the number of patients with improved dyspeptic symptoms

‡ the number of patients with not improved dyspeptic symptoms

**Figure 2. A meta-analysis of seven trials using the DerSimonian and Laird method: Actual drugs (antianxiety or antidepressive agents) vs. placebo for functional dyspepsia. The diamond-shaped box with the horizontal line presents the pooled relative risk and the 95% confidence interval (95% CI).****Figure 3. Bias assessment plot: Active drugs vs. placebo. The bias assessment plot exhibited asymmetry, which indicated both publication and selection bias.**

clic antidepressant agents amitriptyline and mianserin were shown in two placebo-controlled studies (8, 16). In the study with amitriptyline as the actual drug and no medication as the control (17), the effectiveness of amitriptyline was also shown. The mechanisms of the beneficial effects of tricyclic and tetracyclic antidepressant agents for FD are not fully understood. However, the beneficial effects could be attributed not just to their antidepressant properties but also to several actions, such as reducing pain perception (29), and their anticholinergic properties (30). A total of 20% of the patients treated by amitriptyline dropped out of the study because of side effects (16). Although the incidence of side effects among patients taking amitriptyline was high, tricyclic and tetracyclic antidepressant agents may have a beneficial effect in FD patients who do not respond to a first-line treatment like a proton pump inhibitor or prokinetic

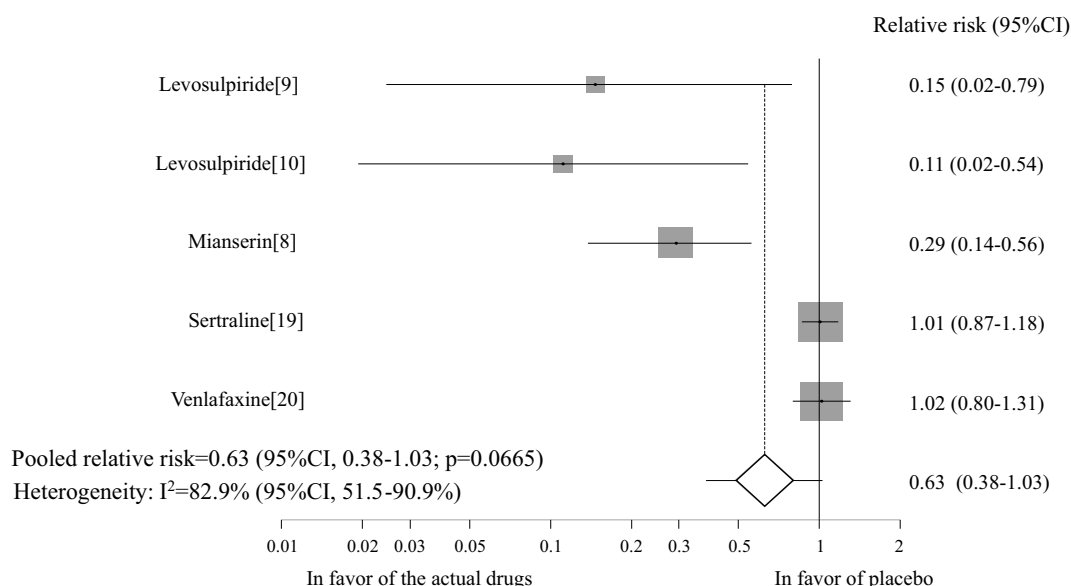


Figure 4. A meta-analysis of five trials using the DerSimonian and Laird method: Actual drugs (antidepressive agents) vs. placebo for functional dyspepsia. The diamond-shaped box with the horizontal line presents the pooled relative risk and the 95% confidence interval (95% CI).

therapy (16). Further clinical studies are necessary to prove the effectiveness of these antidepressant agents. Regarding levosulpiride, we were unable to find any placebo-controlled studies in our current literature search, but a controlled study with cisapride in which the subjects were patients with dysmotility-like FD (18) was newly added in the present review. Dyspeptic symptoms improved significantly in both the group treated with levosulpiride and the group treated with cisapride. There were four randomized controlled studies with levosulpiride in our previous systematic review (9, 10, 31, 32). In these studies, levosulpiride was superior to the placebo. Notably, only 4% of the patients taking levosulpiride dropped out of the study due to side effects (18), which was lower than the drop-out rate of patients in studies of other antidepressants, except mianserin (8). Levosulpiride possesses antidepressant properties as well as prokinetic properties (33, 34). Levosulpiride may have a promising effect on FD; however, levosulpiride is unfortunately not yet available in Japan.

Our previous systematic review showed the effectiveness of anti-anxiety agents or antidepressants for the treatment of FD, and the current review supported the results of the previous review. However, we did not notice the same effectiveness of drugs with antidepressive action in the current review as in the previous review. There are several kinds of psychotropic drugs with anti-anxiety or antidepressive action. These drugs differ in their properties and in safety. Evaluating data obtained from psychotropic drugs of the same type will be necessary to clarify the true effectiveness of these drugs.

Through both systematic reviews, the following possible treatment options for FD were shown: 5-HT_{1A} receptor agonists such as tandospirone may be effective, tricyclic and tetracyclic antidepressant agents may have a beneficial effect

in FD patients who do not respond to first-line treatment, and levosulpiride may have a promising effect on dysmotility-like FD. In clinical practice, these kinds of drugs are recommended for FD patients whose symptoms do not improve with first-line treatment like proton pump inhibitors or prokinetics. Further clinical studies and experience in clinical practice will prove the effectiveness of these drugs.

The authors state that they have no Conflict of Interest (COI).

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