

Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review

Toshi A Furukawa, Hugh McGuire, Corrado Barbui



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Abstract

Objective To compare the effects and side effects of low dosage tricyclic antidepressants with placebo and with standard dosage tricyclics in acute phase treatment of depression.

Design Systematic review of randomised trials comparing low dosage tricyclics (≤ 100 mg/day) with placebo or with standard dosage tricyclics in adults with depression.

Main outcome measures Relative risk of response in depression (random effects model), according to the original authors' definition but usually defined as 50% or greater reduction in severity of depression. Relative risks of overall dropouts and dropouts due to side effects.

Results 35 studies (2013 participants) compared low dosage tricyclics with placebo, and six studies (551 participants) compared low dosage tricyclics with standard dosage tricyclics. Low dosage tricyclics, mostly between 75 and 100 mg/day, were 1.65 (95% confidence interval 1.36 to 2.0) and 1.47 (1.12 to 1.94) times more likely than placebo to bring about response at 4 weeks and 6-8 weeks, respectively. Standard dosage tricyclics failed, however, to bring about more response but produced more dropouts due to side effects than low dosage tricyclics.

Conclusions Treatment of depression in adults with low dose tricyclics is justified. However, more rigorous studies are needed to definitively establish the relative benefits and harms of varying dosages.

Introduction

Despite the growing popularity of selective serotonin reuptake inhibitors and other newer antidepressants, tricyclic antidepressants are still extensively prescribed worldwide. In the United Kingdom between 1991 and 1996 there was a 40% increase in prescriptions for tricyclics for patients starting treatment, with these new patients still outnumbering those taking selective serotonin reuptake inhibitors by 56%.¹ In the United States even today more tricyclics are prescribed than selective serotonin reuptake inhibitors.^{2 3}

Evidence for the recommended dosage of tricyclics is poor.^{4 5} Many of the existing guidelines recommend dosages greater than 100 mg/day or 125 mg/day, but there is a lack of convincing evidence that lower

dosages are not effective.^{6 7} This uncertainty casts doubt on the widely held view that depression is undertreated both in primary care and in psychiatric settings.^{8 9} It also questions whether selective serotonin reuptake inhibitors should be preferred over tricyclics when controlled trials failed to find differences in effectiveness between the two, because it is easier to achieve "adequate" dosage with selective serotonin reuptake inhibitors.¹⁰

Methods

Inclusion criteria

We included randomised trials, lasting at least 4 weeks, comparing low dosage tricyclics with placebo or with standard dosages of the same tricyclic in the acute phase treatment of adults with depression. Low dosage was defined as 100 mg/day or less of imipramine, amitriptyline, clomipramine, desipramine, doxepin, dothiepin, trimipramine, or lofepramine. Standard dosage was defined as greater than 100 mg/day.

Our primary outcome was the effect of treatment on depression, according to the original authors' definition but usually defined as 50% or greater reduction in severity of depression. The severity of symptoms was measured by either observer rating (preferred) or self report.

Identification of trials

We electronically searched the Cochrane Collaboration depression, anxiety, and neurosis controlled trials register up to November 2000 for any trials in which tricyclics were given. Potential papers were examined manually by two reviewers and then checked according to the strict eligibility criteria by two reviewers independently. To identify further trials, references of these selected studies and of other review papers were also checked, representative studies were subjected to SciSearch, and authors and experts were contacted.

Quality assessment and data extraction

The methodological quality of the selected studies was assessed according to the recommendations of the *Cochrane Collaboration Handbook*.¹¹ Data were extracted using data extraction forms by two reviewers independently. Disagreements between them were resolved by consensus.

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Statistical analysis

Data were entered twice into Review Manager (4.1). For dichotomous outcomes, we calculated relative risks and

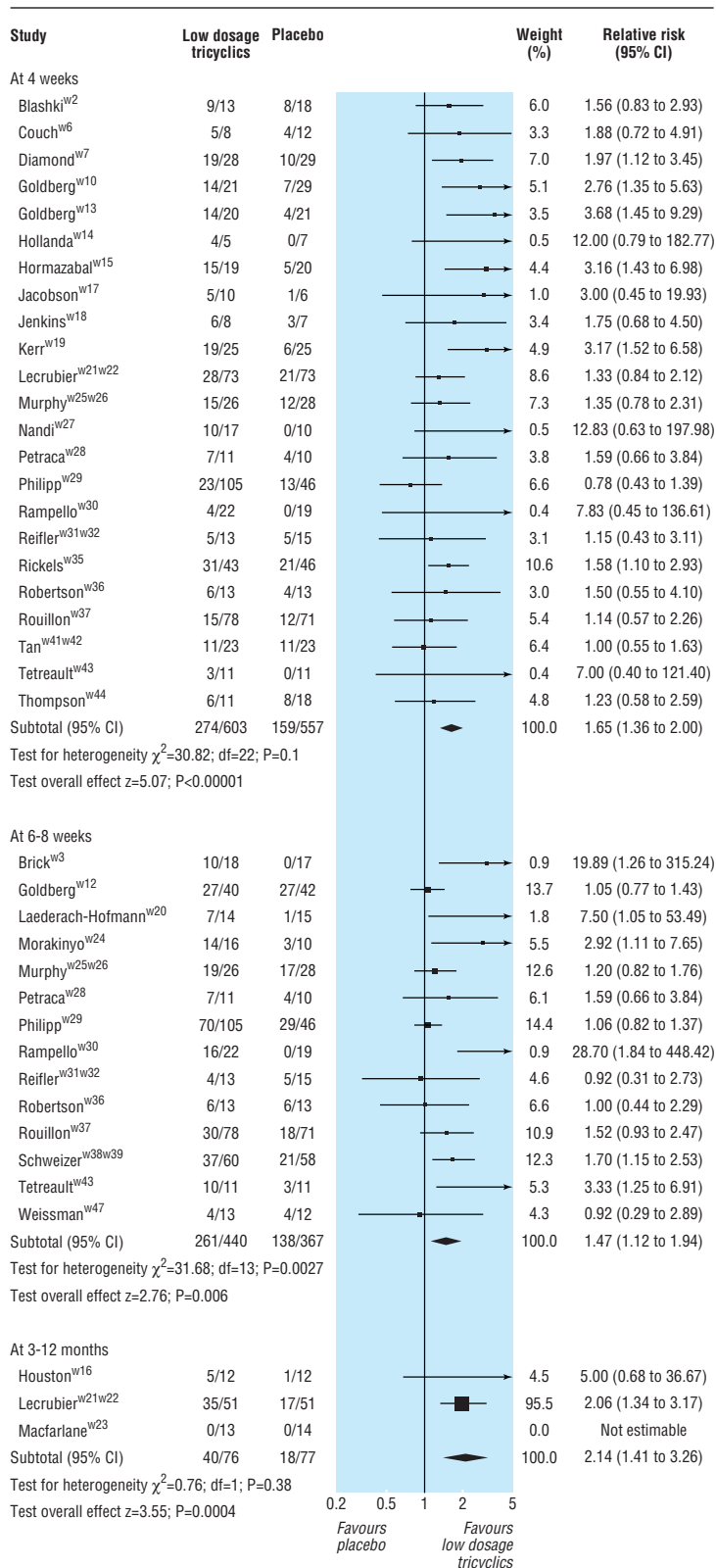


Fig 1 Low dosage tricyclics versus placebo for all depression: per protocol relative risk of response

their 95% confidence intervals with a random effects model.¹²⁻¹³ We assessed heterogeneity between studies with the Q statistic and by visual inspection of the results. For continuous outcomes, we calculated standardised weighted mean differences with a random effects model.

We first performed per protocol analysis according to the values reported by the original authors. When data on dropouts were included we analysed them according to the primary studies. We also performed a worst case scenario intention to treat analysis whereby dropouts were considered non-responders in the active treatment group but as responders in the placebo group.

We performed a funnel plot analysis to check for publication bias. To examine the robustness of the findings we performed two sensitivity analyses, by limiting the included studies to those using operational diagnostic criteria for major depression and to those in which the dosage was less than 75 mg/day.

Results

Study inclusion and characteristics

Of the 2418 citations originally identified in our electronic search, 141 were potentially relevant and were assessed for strict eligibility and quality. We ultimately agreed on 35 studies (2013 participants) that compared low dosage tricyclics with placebo and six studies (551 participants) that compared low dosage tricyclics with standard dosage tricyclics. The inter-rater reliability for this second stage of assessment for eligibility and validity was excellent.

Sixteen studies used amitriptyline as active drugs and 13 used imipramine. Ten studies were conducted in primary care and 12 studies in psychiatric settings. Six studies dealt with depression seen in patients with comorbid physical conditions such as migraine or rheumatoid arthritis. Only four studies reported enough details on their randomisation procedure. (For the complete list of included studies see bmj.com and the Cochrane Library.)

Low dosage tricyclics versus placebo

Effectiveness

Low dosage tricyclics, on average between 75 and 100 mg/day, were 65% (36% to 100%), 47% (12% to 94%), and 114% (41% to 226%) more likely than placebo to bring about response at 4 weeks, 6-8 weeks, and 3-12 months, respectively. Heterogeneity was noted only for the outcome at 6-8 weeks (fig 1).

This advantage of low dosage tricyclics was not maintained when we undertook the strict intention to treat analyses based on the worst case scenario. Effectiveness was, however, maintained when secondary analyses based on continuous measures were carried out. People taking low dosage tricyclics had scores for severity of depression that were 0.29 (0 to 0.59), 0.59 (0.30 to 0.87), 0.59 (0.20 to 0.99), and 0.89 (0.10 to 1.68) standard deviations lower than those taking placebo at 2 weeks, 4 weeks, 6-8 weeks, and 3-12 months, respectively. Heterogeneity was noted for all these time periods (fig 2).

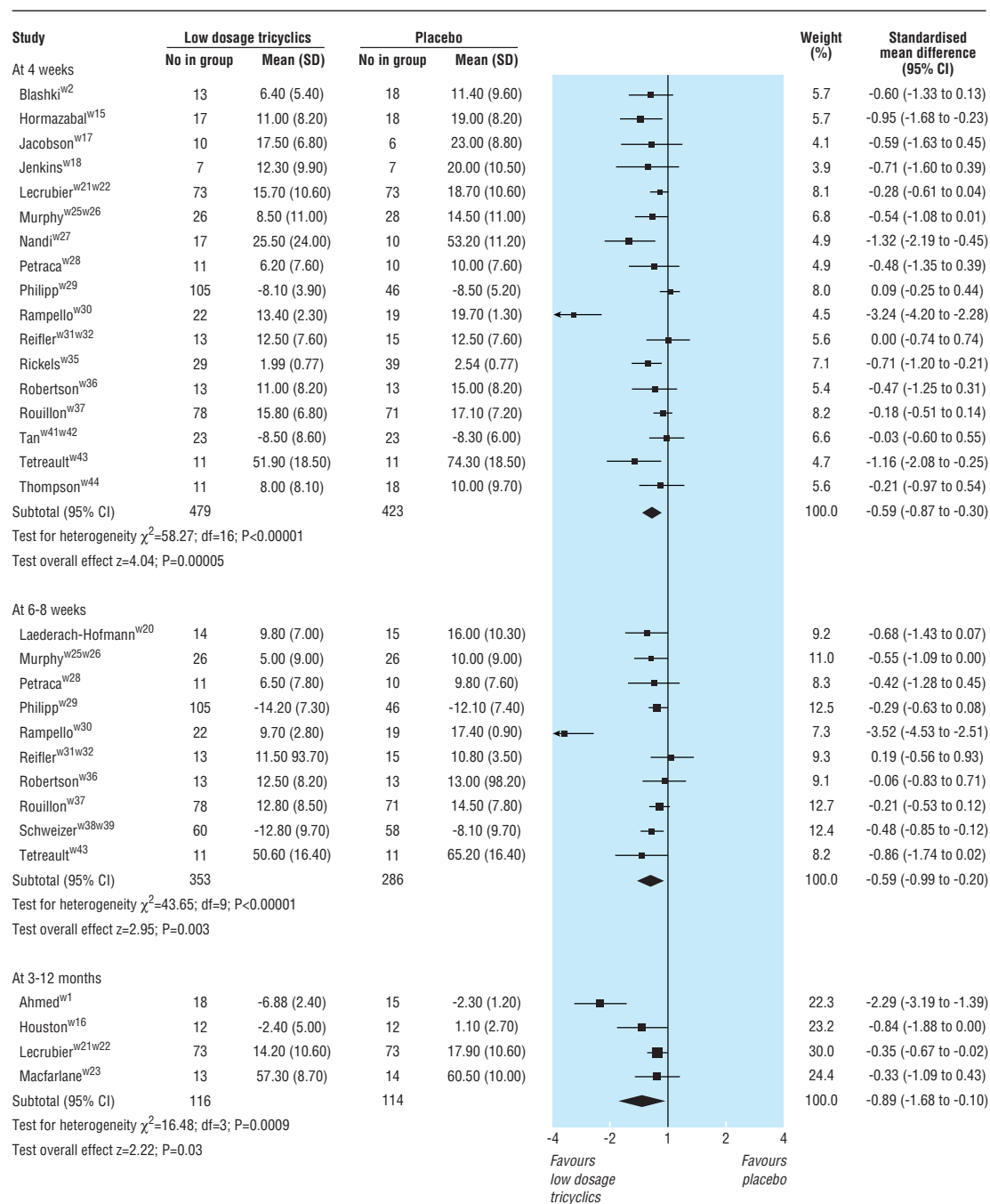


Fig 2 Low dosage tricyclics versus placebo for all depression: per protocol standardised weighted mean difference in depressive severity

Acceptability

No difference was found in total number of dropouts between low dosage tricyclics and placebo groups (relative risk 1.08, 0.93 to 1.26). Overall, 439 of 1840 (24%) enrolled participants dropped out by the end of the trial. People taking low dosage tricyclics, however, were 111% (35% to 228%) more likely than those taking placebo to drop out due to side effects and 63% (36% to 95%) more likely to experience at least one side effect.

Funnel plot analysis and sensitivity analyses

The funnel plot showed some publication bias because the five smallest studies reported large relative risks in

favour of low dosage tricyclics. These studies mainly dated from the 1960s and '70s and involved patients recruited outside a clinical setting. When we omitted these studies the plot was no longer asymmetrical, the relative risk decreased only slightly, and the outcome at 6-8 weeks was no longer heterogeneous. The pooled standardised mean difference for the continuous outcome changed to -0.31 (-0.47 to -0.15) at 4 weeks and -0.32 (-0.49 to -0.15) at 6-8 weeks; these results were also no longer heterogeneous.

When we limited the included studies to those that used operational diagnostic criteria for depression, the results were essentially identical. When we limited the included studies to patients taking less than 75 mg/day

of tricyclics they were still more likely to show response than those taking placebo at 4 weeks (relative risk 1.63, 1.29 to 2.07).

Low dosage tricyclics versus standard dosage tricyclics

Effectiveness

Standard dosage tricyclics were not significantly more effective at achieving response than low dosage tricyclics at 1-8 weeks (fig 3): relative risk 0.89 (0.74 to 1.07) at 4 weeks and 1.11 (0.76 to 1.61) at 6-8 weeks

Acceptability

Overall there was no difference in the acceptability of the treatments when measured by leaving study early for any reason (relative risk 0.95, 0.75 to 1.20). Low dosage regimens, however, were 55% (24% to 73%) less likely than standard dosage regimens to cause dropouts due to side effects.

Discussion

Low dosage tricyclic antidepressants between 75 and 100 mg/day and possibly below this range bring about more reduction in depression at 4-8 weeks of treatment and beyond, as well as more dropouts due to side effects and more people with at least one side effect than placebo in both primary care and psychiatric settings. The number needed to treat to bring about response in depression was between 4 and 6 at 1-6 months of treatment, and the number needed to harm to produce one dropout due to side effects was around 24. Standard dosage tricyclics, however, may or may not be able to bring about more reduction in depression than low dosage tricyclics, although they cause more dropouts due to side effects than placebo (number needed to harm around 11).

What is already known on this topic

Tricyclics are still prescribed as often as selective serotonin reuptake inhibitors and other newer antidepressants worldwide

Experts have often claimed that clinicians prescribe tricyclics at less than adequate dosages

What this study adds

Tricyclics at dosages below the recommended range are more effective than placebo

They may or may not be as effective as standard dosage tricyclics but result in fewer dropouts due to side effects

The minimum effective dosage and ranges for antidepressants has not been established—a simple set of numbers that every practising doctor and patient would want to know

The strength of our conclusions is compromised by several factors. Firstly, the quality of the included studies was not ideal. The success of blinding was not ascertained in any, and many studies did not employ operational diagnostic criteria and interview schedules to diagnose depression. Some studies used ad hoc outcome measures of unknown reliability and validity. Although the dropout rates were not high overall, as our worst case scenario intention to treat analyses showed, they were large enough to hamper drawing definitive conclusions. The dropout is always a problem but here it is even more prominent because, in the case of low dosage tricyclics, there is a trade-off between response and dropouts. If dropouts are not dealt with appropriately, the higher dosage always wins. Secondly, the quality of reporting in the included studies was not ideal. We are uncertain whether random allocation was adequately concealed in most of the studies. Some studies failed to report standard deviations for their outcome measures. Thirdly, and perhaps due to the above factors, we noted heterogeneity for some of the pooled results. A few studies were extreme outliers, all in favour of the low dosage regimen. Lastly, most of the included studies lasted up to eight weeks only.

We evaluated the seriousness of these shortcomings with several sensitivity analyses. Omitting the positive small studies removed heterogeneity of the pooled analyses and yet showed little changes in relative risks and standardised mean differences. Limiting the studies to those that employed modern operational diagnostic criteria or those that used strictly low dosage regimens did not materially affect the pooled estimates of effect sizes.

These sensitivity analyses greatly strengthen the inference that in the treatment of depression, tricyclics at dosages lower than the usually recommended range are more effective than placebo but possibly a little bit less effective than standard dosage tricyclics although with fewer side effects. Every trial protocol should include strategies for ensuring follow up of all the participants even if they stop the prescribed drug, because it is the only way to adhere to the intention to treat

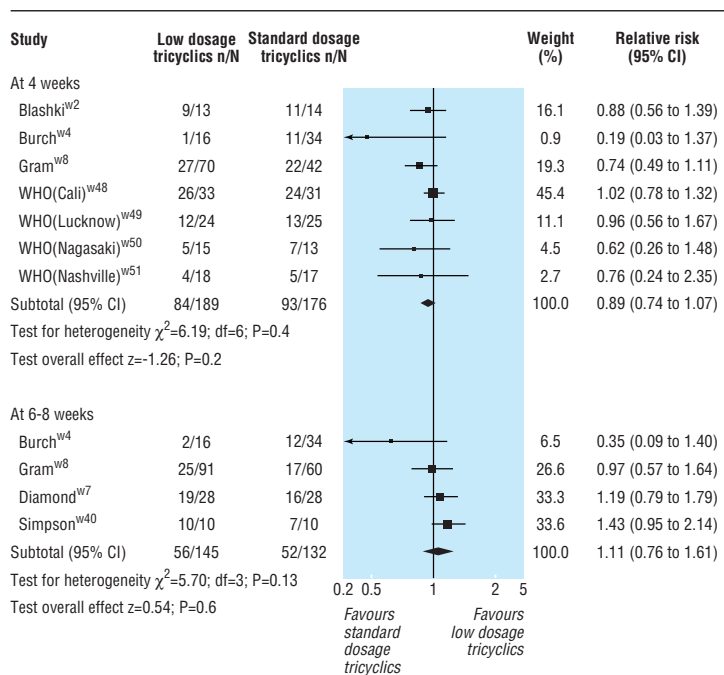


Fig 3 Low dosage tricyclics versus standard dosage tricyclics for all depression: per protocol relative risk of response

principle and to produce results permitting strong inferences about treatment effects.

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Competing interests: TAF has received fees for speaking from several pharmaceutical companies, some of which manufacture various types of antidepressants including paroxetine, fluoxetine, and milnacipran.

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Incidence of fires and related injuries after giving out free smoke alarms: cluster randomised controlled trial

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Abstract

Objective To measure the effect of giving out free smoke alarms on rates of fires and rates of fire related injury in a deprived multiethnic urban population.

Design Cluster randomised controlled trial.

Setting Forty electoral wards in two boroughs of inner London, United Kingdom.

Participants Primarily households including elderly people or children and households that are in housing rented from the borough council.

Intervention 20 050 smoke alarms, fittings, and educational brochures distributed free and installed on request.

Main outcome measures Rates of fires and related injuries during two years after the distribution; alarm ownership, installation, and function.

Results Giving out free smoke alarms did not reduce injuries related to fire (rate ratio 1.3; 95% confidence interval 0.9 to 1.9), admissions to hospital and deaths (1.3; 0.7 to 2.3), or fires attended by the fire brigade (1.1; 0.96 to 1.3). Similar proportions of intervention and control households had installed alarms (36/119 (30%) *v* 35/109 (32%); odds ratio 0.9; 95% confidence interval 0.5 to 1.7) and working alarms (19/118 (16%) *v* 18/108 (17%); 0.9; 0.4 to 1.8).

Conclusions Giving out free smoke alarms in a deprived, multiethnic, urban community did not reduce injuries related to fire, mostly because few alarms had been installed or were maintained.

Introduction

Residential fires caused 466 deaths and 14 600 non-fatal injuries in the United Kingdom in 1999.¹ The risk of

death from fire is associated with socioeconomic class,² partly because of social differences in the risk factors for fires and in ownership of smoke alarms. The risk of death in a house fire is three times higher in homes without smoke alarms.³ A controlled study before and after distribution of free smoke alarms to households in one area at high risk in Oklahoma City, United States, showed an 80% drop in hospitalisations and deaths related to fire, while morbidity and mortality related to fire in the rest of the city did not change,⁴ but these findings may not apply in other settings.

To quantify the effect of giving out free smoke alarms on fires and related injuries, we conducted a cluster randomised controlled trial, in a deprived multiethnic urban population.

Methods

The study took place in two inner London boroughs with a total of 330 000 residents, of whom 51% (168 300) lived in council or other social housing and 18% were from a minority ethnic group. The mean Jarman score, a measure of material deprivation and increased healthcare needs,^{5,6} was more than two standard deviations greater than the national mean.

Study design and randomisation

We pair matched 40 electoral wards by Jarman score and randomly allocated wards in pairs to intervention and control groups. The 40 studied wards contained between 2179 and 5586 (mean 3686) households and between 5205 and 12 661 (8191) residents.

Intervention

In coordination with the local health authority, the programme distributed 20 050 smoke alarms, with

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