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Prevalência de *dropout* em ensaios clínicos randomizados no tratamento de adolescentes com depressão e fatores associados: uma revisão sistemática e metanálise

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Dissertação submetida ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do grau de Mestre.

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RESUMO

Introdução: A depressão afeta 350 milhões de pessoas, sendo que a prevalência para os adolescentes é de 4 a 5%. O tratamento auxilia na remissão dos sintomas e na cura, propiciando a melhora em vários aspectos da vida. O paciente que abandona (*dropout*) o tratamento ou ensaio clínico não é acompanhado e monitorado pela equipe médica. **Objetivo**: Identificar as taxas *dropout* de ensaios clínicos randomizados com adolescentes deprimidos em tratamento farmacológico e fatores associados ao abandono. **Métodos**: Foram buscados nas bases (Medline, Embase, Cochrane, Clinical Trial, Psycinfo e Web of Science) artigos com os *mesh terms* "depressive disorder", "randomized trials" e "adolescents". A qualidade dos estudos foi medida por meio das escalas *Cochrane Handbook for Systematic Reviews of Interventions* e Jadad. Os dados quantitativos extraídos para análise foram: *dropout* geral e por grupos (intervenção e controle). Foram realizadas subanálises para verificar a prevalência de *dropout* em relação à faixa etária, classe de medicamento antidepressivo e tipo de intervenção (usual ou combinada). A análise qualitativa identificou fatores associados às taxas de *dropout*. **Resultados**: A amostra final totalizou 50 artigos, sendo que 42 apresentavam taxas de *dropout*. A prevalência geral de *dropout* foi de 23% (IC 95% 20-27), $p < 0,0001$, com heterogeneidade (I^2) de 94,2%. Participantes acima de 16 anos, pacientes tratados com ISRN e aqueles que receberam apenas medicamentos apresentaram maior taxa de *dropout,* respectivamente (33% (IC 95% 27-39), (45% (IC 95% 31-64) e (15% (IC 95% 13-17)). A prevalência de *dropout* estava mais associada aos efeitos adversos, problemas relacionados aos ensaios clínicos e intervenção familiar. **Discussão**: Um estudo com adolescentes com depressão resistente e outro que tratava os participantes com duloxetina, apresentaram maior prevalência de *dropout*. Medicamentos ISRN foram responsáveis por maior taxa de abandono, mesmo não sendo indicado para adolescentes. A terapia cognitivo-comportamental combinada à farmacoterapia demonstrou menor prevalência de *dropout*, pois visa a mudança de comportamento, desenvolvimento de habilidades e encorajamento. A prevalência de *dropout* foi maior no grupo com mais de 16 anos explica-se pela autonomia e responsabilidade sobre o seu tratamento. Efeitos adversos associaram-se mais às taxas de *dropouts*. Isto explica-se pela pouca seletividade, mas também por características pessoais do paciente. **Conclusão**: Alta prevalência de *dropout* estava associada aos efeitos adversos aos medicamentos. As subanálises mostraram que estudos com ISRN, tratamento apenas com medicamento e adolescentes com maior de 16 anos têm maior taxa de abandono.

Palavras-chave: adolescentes, depressão, antidepressivos e não adesão

ABSTRACT

Introduction: Depression currently affects 350 million people and the prevalence for teenagers is 4 to 5%. Treatment with antidepressants, when properly adhered, helps in remission of symptoms and healing, leading to improvement in various aspects of your life. The dropout of treatment or a clinical trial the adolescent is not accompanied by the medical team, which monitors your signs and symptoms as well as the lack of adherence and their causes. **Objective**: Identify the dropout rates in randomized clinical trials with depressed adolescents in drug treatment and factors associated with dropout, summarizing this information in a systematic review and meta-analysis. **Methods**: We searched the databases (Medline, Embase, Cochrane, Clinical Trial, Psycinfo and Web of Science) articles with the mesh terms "depressive disorder", "randomized trials" and "adolescents". The evaluation of the quality of the studies was through the Cochrane Handbook for Systematic Reviews of scales Interventions and Jadad. Quantitative data extracted for analysis were: age, type of intervention, general dropout and groups (intervention and control). Sub-analyzes were performed to determine the prevalence of dropout in terms of age, antidepressant class and type of intervention (usual or combined). The qualitative analysis occurred for identifying and categorizing the factors associated with dropout rates. The prevalence of dropout was associated with more adverse effects, problems related to clinical trials and family intervention. **Discussion**: This study demonstrated a high prevalence of dropout. One of the studies had higher prevalence of dropout investigated adolescents with resistant depression and other used duloxetine, reasons that can explain this fact. The drug of medicines that had the highest dropout rate was SNRI, although this type of medication is not recommended for adolescents. Cognitive-behavioral therapy combined with pharmacotherapy showed lower prevalence of dropout, as this intervention works on behavior change, skill development and encouragement. The prevalence of major dropout in the group with more than 16 years explained by the fact that teens have more autonomy and responsibility for their treatment. Adverse effects was the most associated with dropouts factor, which occurs with drugs with little selectivity, but also for the patient's personal characteristics. Conclusion: There was a high prevalence of dropout which was associated with adverse effects to drugs. The sub-analyzes showed that studies with SNRI, treatment with medication and adolescents over 16 years had a higher dropout rate.

Key words: adolescents, depressive disorder, antidepressants and dropout.

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5 – HT – Serotonina
ATC – Antidepressivo Tricíclico
BDI - *Beck Depression Inventory*
DALY - *Disability Adjusted Life Years*
DSM – V - Diagnostic and Statistical Manual of Mental Disorders
ECA – Estatuto da Criança e do Adolescente
FDA – *Food and Drug Administration*
IMAO – Inibidor Seletivo da Recaptação de Serotonina
ISRN – Inibidor Seletivo da Recaptação de Noradrenalina
ISRS – Inibidor Seletivo da Recaptação de Serotonina
OMS – Organização Mundial da Saúde
SIDA – Síndrome da Imunodeficiência Adquirida
TCC – Terapia Cognitivo-comportamental

SUMÁRIO

1 INTRODUÇÃO

1.1 Epidemiologia da depressão e aspectos sintomatológicos

O transtorno depressivo vem se mostrando uma doença cada vez mais evidente na população ao longo dos tempos, afetando atualmente de 350 milhões de indivíduos. Um estudo conduzido pelo *World Mental Health Survey* em 17 países mostrou que em média uma em cada vinte pessoas tem episódio de depressão. Estimativas apontam que em 2020, a depressão alcançará o segundo lugar na classificação do DALYs (*Disability Adjusted Life Years*), o qual mede o número de dias de vida perdidos devido à morte precoce e a quantidade de dias improdutivos em vida decorrentes da incapacidade da doença em questão. Na sua forma mais grave, a depressão pode causar suicídio, causando um número estimado de um milhão de mortes por ano. Em se tratando de adolescentes, a Organização Mundial da Saúde refere que no ano de 2012 o suicídio foi a terceira maior causa de mortes entre esta população, perdendo apenas para acidentes automobilísticos e HIV. Entre o período de 2000 a 2012, a depressão se mostrou como primeira colocada do DALYs para adolescentes (WHO, 2012; WHO, 2014).

Estudos apontam que a prevalência de depressão na adolescência é similar a de adultos (4-5%) (COSTELLO et al, 2005; COSTELLO et al, 2006). Lewinshon (1999) e Hankin (1998), apontam uma probabilidade de elevação em torno de 5% na fase inicial da adolescência e de 20% no período final, variando muito de um país para outro devido as diferenças de metodologias utilizadas nas pesquisas (FLEITLICH & GOODMAN, 2004; LOPEZ et al, 2006; PILLAI et al, 2008).

Em uma pesquisa (Pesquisa Nacional de Comorbidades) nos Estados Unidos, realizada por Kessler e Walter (1998) com 1769 adolescentes de 15 a 24 anos, foi identificada a prevalência da depressão para sexo feminino (12,4%) sobre o masculino (1,5%). Já no Brasil, um estudo transversal entre novembro de 2005 e abril de 2006, com 3007 indivíduos maiores de 14 anos, verificou a presença de sintomas depressivos predominante no sexo feminino (28.3%), sendo que a população de adolescentes de 14 a 17 anos com depressão maior representou 25% (COELHO et al, 2013). Ao encontro destes achados, um estudo de metanálise que possuía como intuito principal investigar a prevalência de sintomas depressivos no Brasil, concluiu que mulheres brasileiras com depressão representam 17% (SILVA et al, 2014). O DSM-V (Manual Diagnóstico e Estatístico de Transtornos Mentais)

menciona que as mulheres têm índices 1,5 a 3 vezes mais altos que os homens, sendo que o início ocorre na adolescência (APA , 2014).

A depressão é uma doença na qual há perda do interesse ou prazer por quase todas as atividades e humor deprimido por, no mínimo, duas semanas seguidas. De acordo com o DSM-V, o aspecto essencial do transtorno depressivo maior é uma evolução clínica, caracterizada por um ou mais episódios depressivos sem uma história de episódios maníacos, mistos ou hipomaníacos. Em crianças e adolescentes, esta forma de humor pode manifestar-se por irritabilidade, em vez de tristeza (APA, 2014).

Os sintomas da depressão estão categorizados em quatros conjuntos: marcadores emocionais (tristeza, isolamento, perda da capacidade de experimentar prazer em atividades já consideradas agradáveis, crises de choro, sentimentos de desvalorização e culpa inadequados e variação de humor diurno); cognitivos (distração, falta de capacidade na tomada de decisões, superestimação das perdas sofridas, pessimismo e desesperança); motivacionais (indiferença diante de novas situações, desinteresse por qualquer atividade, perda da afeição por outras pessoas e baixo rendimento escolar); e vegetativos ou motores (fadiga, retardo psicomotor, alterações de apetite ou do peso, insônia e perda da libido). Vale salientar que a adolescência é uma fase marcada por mudanças corporais e comportamentais (agitação, ataques de raiva, delinquência, agressividade uso de drogas e queixas de dor crônica), as quais podem mascarar a depressão (LEWIS e WOLKMAR, 1993; KESSLER, 2001; DUTRA, 2002).

O primeiro episódio de depressão pode ocorrer em qualquer idade. No entanto, na metade da adolescência até o fim dos 20 anos há uma maior probabilidade do surgimento, o que está relacionado positivamente com a sua cronicidade, demonstrando ser um fator de risco (HÖLZEL, 2011; APA, 2014). Além deste, há outros fatores que predizem a depressão, os quais estão expostos na figura 1.

De acordo com a renda, Coelho e colaboradores (2013) concluíram que a depressão maior é mais prevalente em indivíduos com baixa renda e níveis de escolaridade. Segundo o grupo *Quality of Life Assessment,* da OMS, a qualidade de vida é definida pela percepção do indivíduo sobre a sua posição na vida, no contexto cultural e dos sistemas de valores em relação a sua perspectiva, objetivos, padrões

e preocupações. Indivíduos que se percebem com baixo nível de qualidade de vida possuem mais sintomas depressivos (OMS, 1995).

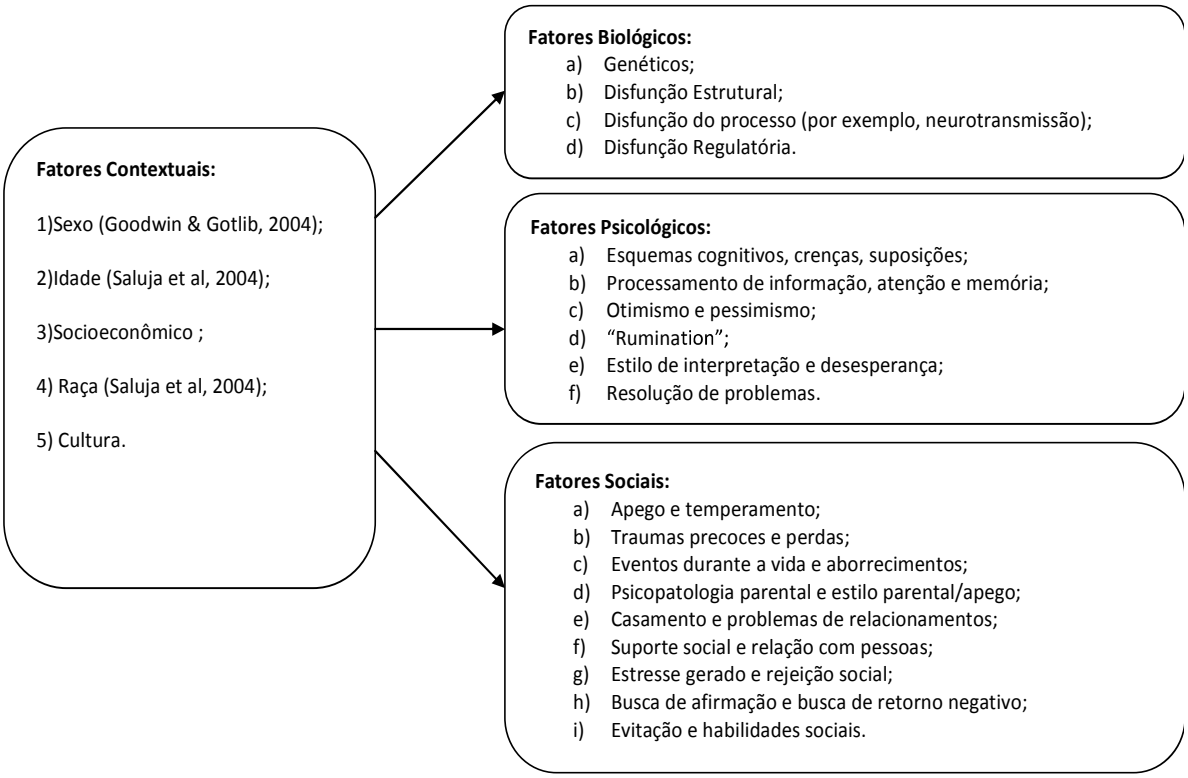

Figura 1. Fatores de Risco para Depressão (Adaptado de Dobson & Dozois, 2008)

Do ponto de vista fisiológico, os sintomas da depressão se relacionam com os níveis de neurotransmissores (hipótese da amina biogênica), onde o decréscimo de norepinefrina causa a perda de energia, de atenção e de interesse pela vida; ansiedade, baixa autoestima, insegurança, obsessão e compulsão, relacionam-se com a queda da serotonina; e baixos níveis de dopamina reduzem a atenção, motivação, prazer e interesse pela vida. No entanto, a literatura também revela outras alterações fisiopatológicas, que são: modificações pós-sinápticas na sensibilidade dos receptores de norepinefrina ou de serotonina e que estão relacionados com o início da depressão; falha na regulação homeostática dos sistemas neurotransmissores, os quais conduzem a um aumento ou diminuição das suas atividades; funcionalidade dos sistemas noradrenérgicos e serotonérgicos que devem estar aptos para que haja um efeito antidepressor; e, finalmente, o papel da dopamina no *nucleus accumbens* que relaciona-se com um mecanismo antidepressor, em condições elevadas (WELLS et al, 2006; WANNMACHER, 2011).

Situações de estresse geram uma resposta alostática excessiva ou ineficaz, desencadeando uma carga, que por sua vez, obriga um reajuste do seu sistema psicofisiológico interno ao meio externo, custando cada vez mais a ele adaptar-se, buscando a homeostase. Esta adaptação obrigatória do organismo, o afeta tanto na forma estrutural quanto na funcional, especificamente nas regiões encefálicas pré-frontais e na regulação do sistema hipotálamo-hipófise-adrenal (HPA) (KAPCZINSKI et al, 2008).

1.2 Adolescência

A adolescência, de acordo com Estatuto da Criança e do Adolescente – ECA (1990) - no Brasil, é o período entre 12 e 18 anos incompletos. No entanto, Organização Mundial da Saúde, adolescente é a pessoa que se encontra entre 10 aos 19 anos (*World Health Organization*, 2014). Este período da vida geralmente é dividido em três fases: a inicial, que compreende a fase dos 11 aos 14 anos; a intermediária, dos 14 aos 17 anos; e a final, dos 17 aos 20 anos. Faz-se necessário ressaltar que o crescimento do adolescente nesta fase abrange um longo tempo e que esta divisão varia muito de um indivíduo para outro (ISOLAN et al, 2009).

Esta fase caracteriza-se por mudanças bruscas de desenvolvimento biológico, psicológico e social. Quanto às transformações biológicas, pode-se afirmar que há um rápido crescimento esquelético e sexual, iniciando a puberdade e concluindo a capacidade reprodutiva. Os primeiros sinais externos são os seios e os pelos pubianos nas meninas, enquanto que nos meninos, há o aumento dos testículos. Alguns meninos experimentam um aumento temporário das mamas, o que gera sofrimento; porém, esse problema pode se resolver em até 18 meses. O aparecimento de pelos nas meninas também é motivo de desconforto. A voz dos meninos se torna mais grave, a pele mais grossa e mais oleosa e consequentemente há aumento das glândulas sebáceas, originando cravos e espinhas. Concomitantemente, ocorre a maturação dos órgãos reprodutores, trazendo a menstruação nas meninas e a produção de espermatozoides nos meninos (SUSMAN & ROGOL, 2004; PAPALIA et al, 2009).

O impulso de crescimento geralmente inicia entre os 9 anos e meio e os 14 anos e meio para o sexo feminino, enquanto que para o sexo masculino acontece entre os 10 anos e meio e os 16 anos. Tendo em vista que o crescimento ocorre

dois anos mais cedo nas meninas, elas estão propensas a serem mais altas, mais pesadas e mais fortes entre os 11 e 13 anos. Após este surto de crescimento, os meninos ficam novamente maiores (PAPALIA et al, 2009). O acelerado desenvolvimento psicológico é marcado pelo crescimento cognitivo havendo, portanto, uma consolidação da formação da personalidade. Socialmente, a adolescência é um período de preparo intensivo para a próxima fase do ciclo vital, que é a fase do adulto-jovem (ISOLAN et al, 2009; PAPALIA et al, 2009).

O adolescente encontra no decorrer do seu desenvolvimento algumas situações difíceis, tais como: despertar para a psicossexualidade (desejos sexuais ligados à pessoa amada), inconsequência na autovalorização (sentimentos contraditórios que oscilam, provocando tendência para depressão, rebeldia, suscetibilidade excessiva e vulnerabilidade à crítica), ambivalência perante sua emancipação (desejo de liberdade ao mesmo tempo em que pede amparo aos pais/responsáveis), instabilidade e agudização das emoções (propensão ao extremismo nas experiências emocionais) (ABERASTURY & KNOBEL, 1986).

Há pouco tempo, acreditava-se que o desenvolvimento cerebral estava amadurecido na puberdade, no entanto, alterações importantes ocorrem até os 40 anos de idade, as quais envolvem emoções, julgamento, organização do comportamento e autocontrole. O cérebro, durante a adolescência, perde densidade de massa cinzenta (neurônios compactados) em certas regiões do córtex cerebral, compensada pelo aumento da massa branca, axônios ou fibras nervosas que transmitem informações entre os neurônios e as regiões distantes do cérebro. Paralelamente, é acrescido mielina nas conexões, começando nos lobos frontais e movendo-se em direção à parte posterior do cérebro. Em contrapartida, a perda da massa cinzenta parece mover-se brutalmente no sentido oposto (PAPALIA et al, 2009).

Em um estudo longitudinal de 13 indivíduos de 4 a 21 anos, o declínio de massa cinzenta começou entre 4 e 8 anos de idade nas regiões responsáveis as atividades básicas sensorial e motora; depois, por volta de 11 a 13 anos, direcionou-se na direção de trás para frente para as áreas dos lobos parietais envolvidas com a atenção, linguagem e orientação espacial; e, finalmente, na adolescência tardia para as áreas do córtex pré-frontal, que controlam o raciocínio e outras funções importantes (PAPALIA et al, 2009). Em um estudo conduzido por de Bellis et al (2001) com 61 meninos e 57 meninas, foi possível notar que os primeiros tem uma

perda de massa cinzenta significativa e aumento da massa branca e de filamento de corpo caloso. As meninas também demonstraram essas modificações, mas em proporção mais lenta.

Isso pode explicar a tendência que os adolescentes têm para explosões emocionais e comportamentos arriscados, como uso de drogas e aceitação de riscos sexuais. A imaturidade do cérebro pode permitir que sentimentos se sobreponham à razão e impedindo que alguns adolescentes prestem atenção a perigos que parecem óbvios para os adultos (BAIRD et al, 1999; YURGELON-TODD, 2002).

1.3 Depressão na adolescência

O interesse pela depressão em adolescentes é recente, pois até a década de 70 julgava-se que ela fosse rara. Dentre a população com algum distúrbio depressivo, a fração que representa os adolescentes é significativa, afinal é nesta fase que ocorrem mudanças aceleradas e profundas acerca da sua maturidade psicológica e de seu crescimento físico, acarretando na perda de um semblante infantil e que ainda não adquiriu características adultas (BALHS, 2002). Em um estudo realizado por Gorenstein et al (2005) com 1555 adolescentes brasileiros, constatou-se a prevalência de 7,6% de depressão nesta população, de acordo com o instrumento BDI (*Beck Depression Inventory*). Além deste, Coelho et al (2013) apresentou a prevalência de 25% de sintomas depressivos em adolescentes de 14 a 17 anos.

A depressão na adolescência pode apresentar-se com um humor deprimido, incapacidade de sentir prazer, fadiga, sentimentos de culpa ou inutilidade, diminuição da concentração, alterações de sono e apetite (redução ou aumento), agitação ou retardo psicomotor, alterações de conduta, abuso de drogas e irritabilidade e pensamentos recorrentes de morte. O diagnóstico é estabelecido quando cinco ou mais dos sintomas supracitados estiverem presentes por, no mínimo, duas semanas, sendo que um dos sintomas deve ser humor deprimido (em adolescentes pode-se substituir por irritação) ou perda de interesse ou prazer (ZAVASCHI, 2009; APA, 2014).

Existem fatores de risco e de proteção para o aparecimento da depressão em adolescentes. Os primeiros, dizem respeito à condições que favorecem o surgimento

da doença em questão, ao contrário dos determinantes de proteção (CAIRNS et al, 2014). Em uma metanálise de estudos longitudinais, realizada por Cairns et al (2014), que teve como intuito encontrar fatores de risco e proteção para depressão em adolescentes, pôde-se concluir que o uso de drogas lícitas e ilícitas, seguir dieta nutricional, ter estratégias negativas de enfrentamento e ganho de peso, são fatores que predispõem a depressão.

Como outros distúrbios de saúde, vários fatores interagem para aumentar o risco para desenvolver a depressão. A avaliação da contribuição de cada fator de maneira isolada em determinados momentos da vida é muito difícil, pois fatores de risco sociais, familiares e individuais estão fortemente correlacionados (THAPAR et al, 2012). Determinantes hereditários e adversidades no início da vida podem, direta ou indiretamente, predispor a depressão, mediando os efeitos por meio de temperamento, personalidade (emoção negativa, baixa emoção positiva, controle da atenção, comportamento inibido e neuroticismo) e cognição (GARBER, 2006). Aliado a isso, a maturidade e as mudanças hormonais podem alterar a sensibilidade individual a efeitos estressores.

Filhos de pais, os quais tiveram depressão, possuem de 3 a 4 vezes mais chance de ter a doença quando comparadas a filhos de pais saudáveis (RICE et al, 2002). rGE é um gene definido como influente genético em relação à exposição ambiental e confirma que fatores genéticos e ambientais não são independentes (PLOMIN et al, 2008). Alguns estudos com gêmeos demonstraram que tal gene pode estar presente na negatividade familiar, que incluem sentimentos de raiva, hostilidade e conflitos. Há relatos na literatura que o rGE também tem relação entre fatores familiares adversos, implicando em negatividade parental e atos disciplinares punitivos, com a depressão em adolescentes (NEIDERHEISER et al, 1999; LAU & ELEY, 2008). Outros estudos sugerem que uma variante (5-HTTLPR) no transporte da serotonina pode aumentar o risco para depressão, mas apenas na presença de eventos estressores ou maus-tratos precoces (CASPI et al, 2003; UHER & McGUFFIN, 2009).

Muitas pesquisas foram realizadas para compreender a relação da depressão com fatores ambientais, como: eventos estressores (por exemplo, lesão corporal e luto) e adversidades crônicas (maus-tratos, discórdia familiar, *bullying*, pobreza e doenças físicas). Todavia, tais exposições não conduzem ao desenvolvimento da depressão em adolescentes, embora aqueles que tenham alto risco genético são

mais suscetíveis aos efeitos nocivos de tais eventos adversos (GOODYER et al, 1990; PINE et al, 2002; HARIRI et al, 2002). Os eventos estressores estão mais fortemente associados com o primeiro episódio de depressão do que com a sua recorrência e o risco é consideravelmente maior nas meninas e em adolescentes que estão expostos a múltiplos eventos (FLEITLICH-BILYK & GOODMAN, 2004; PARKER & BROTCHIE, 2010).

1.4 Tratamento da depressão em adolescentes

As intervenções clínicas eficazes para transtornos depressivos disponíveis incluem terapia cognitivo-comportamental (TCC) e farmacológica, sendo a primeira de escolha inicial. Estudos revelam que a terapia cognitivo-comportamental é provavelmente mais eficaz em adolescentes com formas leves de depressão, mas não consegue produzir de forma consistente os efeitos benéficos em níveis elevados da doença (WEISZ et al, 2006; KLEIN et al, 2007; BRENT et al, 2008). Em contrapartida, um estudo denominado Estudo de Tratamento para Adolescentes com depressão, nos Estados Unidos, comprovou que 12 semanas de tratamento combinado com antidepressivo (fluoxetina) e terapia cognitivo comportamental produz melhoras significativas quando comparado ao medicamento administrado unicamente (MARCH et al, 2004).

Há três questões que merecem destaque em relação ao tratamento da depressão em adolescentes. A primeira refere-se à diferença que há entre tratar depressão em adolescentes e adultos. A segunda, as melhores práticas clínicas são controversas, pois as diretrizes clínicas variam entre os países, já que há uma preocupação sobre o uso de antidepressivos em indivíduos menores de 18 anos. E, finalmente, a terceira, há evidências de tratamentos psicológicos e medicamentosos a curto prazo, mas informações a respeito de tratamento a longo prazo e crises recorrentes são escassas na literatura atual (THAPAR et al, 2012).

Está consolidado na literatura que os antidepressivos da classe inibidores da recaptação de serotonina (ISRS) são os mais prescritos devido a seu perfil de efeitos adversos significativamente mais seguro, em especial, por reduzir efeitos cardiotóxicos e a letalidade de intoxicação por doses excessivas em comparação aos riscos associados aos antidepressivos tricíclicos. A FDA (*Food and Drug Admnistration*) aprovou a fluoxetina para tratamento depressão maior em pessoas

com 8 anos ou mais (GREEN, 2008). Além disso, ensaios clínicos randomizados apontam que o escitalopram também pode ser efetivo, o que levou a FDA aprovar o seu uso em adolescentes (EMSLIE et al, 2009).

O risco de suicídio em pessoas que se tratam com antidepressivos é um tanto controverso, pois pesquisas realizadas, incluindo metanálise, sugerem uma associação significativa, especialmente em jovens (HETRICK et al, 2007; BRIDGE et al, 2007) . Indivíduos com menos de 25 anos estão mais propensos a desenvolver pensamentos suicidas. Entretanto, um estudo de metanálise (BRIDGE et al, 2007), mostrou que os benefícios do tratamento com antidepressivos superam os riscos, uma vez que há evidências mistas acerca do risco de suicídio quando utilizado medicamento antidepressivo para o tratamento da depressão, recomenda-se monitorar estes riscos, independente da opção de tratamento (THAPAR et al, 2012).

O período da adolescência, como já se conhece, é marcado por bruscas mudanças fisiológicas e, consequentemente, os aspectos farmacocinéticos (absorção, distribuição, metabolismo e excreção) também estão alterados. Diante disso, tanto adolescentes quanto crianças, exigem doses mais altas de medicamentos para que alcancem resultados terapêuticos e níveis séricos equivalentes aos de um adulto, pois o metabolismo hepático está mais acelerado (atividade dos CYPs elevada) e a filtragem glomerular aumentada (BRASIL, 2000; BRENT & BIRMAHER, 2002; ROCHA et al, 2004).

1.5 Adesão ao tratamento farmacoterapêutico

A questão da adesão à terapia farmacológica tem sido muito discutida ao longo dos tempos, por ser um fator de extrema importância para o êxito do tratamento. Até mesmo Hipócrates, em seus estudos, já fazia alusão ao tema, afirmando que seus pacientes mentiam ao dizer que seguiam exatamente o que lhes tinha sido indicado. Esta falha da farmacoterapia tem como consequência não somente o insucesso do tratamento, mas também possíveis danos adicionais ao paciente. Nos Estados Unidos, observou-se que a não adesão provoca em torno de 125 mil mortes anualmente e custa, ao sistema de saúde deste país, cerca de 100 bilhões por ano (DADER et al, 2008; DARBISHIRE et al, 2012; LEITE & VASCONCELLOS, 2003; OSTEBERG & BLASCHKE, 2005).

O conceito adesão foi explicado em meados do século 20 por Haynes como sendo o grau em que o comportamento do doente (tomar medicação e cumprir outras prescrições médicas como dieta e mudança de estilo de vida) coincide com a prescrição clínica (CORREIA-TELLES et al, 2007). Entretanto, para outros autores, a adesão significa a utilização dos medicamentos prescritos ou outros procedimentos em pelo menos 80% de seu total, observando sempre a posologia e ou, ainda, um complexo de fenômenos que envolvem a decisão do paciente em seguir ou não a prescrição de medicamentos e demais procedimentos (CARDOSO & GALERA, 2006; LEITE & VASCONCELLOS, 2003; WHO, 2003).

Primeiramente, para tratar da adesão, Haynes utilizava a palavra *compliance* que, na língua inglesa, traduz-se como “condescendência/cumprimento/submissão”. Devido a sua conotação submissa e coercitiva, pressupondo um nível hierárquico entre médico e paciente, onde o segundo assumiria uma postura passiva, este termo foi abandonado em favor do termo *adherence* (em português, adesão, consentimento, ou aderência), subentendendo uma relação maior de igualdade entre médico e paciente. No entanto, a *Royal Pharmaceutical Society of Great Britain* adotou o vocábulo *concordance* que, na língua portuguesa, corresponde a “concordância”, “consentimento” ou “conformidade”, indicando assim, uma aliança terapêutica mais próxima (CARDOSO & GALERA, 2006; CORREIA-TELLES et al, 2007; HOUAISS & CARDIM, 1998).

Alguns estudos apontaram os motivos para a não adesao à terapia farmacológica (DIAS et al, 2011; OSTEBERG & BLASCKE, 2005). Cita-se as questões relacionadas ao regime farmacoterapêutico, relato do paciente, relato da medicação e planos de adesão, a falta de acesso ao medicamento, alto custo, quantidade de medicamentos prescritos (quanto maior o volume de medicamentos, menor a taxa de adesão), esquema terapêutico (adaptação da rotina para seguir a posologia) efeitos colaterais, a própria doença, ausência de sintomas, presença de problemas fisiológicos (particularmente a depressão), falta de conhecimento do paciente a respeito da sua doença, relação com o profissional da saúde e atitudes do profissional prescritor (linguagem, tempo da consulta, atendimento acolhedor, respeito com as verbalizações do paciente e seus questionamentos e motivação para o cumprimento). Ainda, estudiosos abordam a opinião negativa da família e amigos do paciente como um motivo importante para a baixa adesão (BARROS & BARROS, 2010; CARDOSO & GALERA, 2005; DARBISHIRE et al, 2012; KURITA &

PIMENTA, 2003; LEITE & VASCONCELLOS, 2003; OSTEBERG & BLASCKE, 2005).

Em um estudo conduzido com 24 pacientes de uma unidade de saúde mental, que apresentavam transtorno depressivo unipolar, foi possível detectar fatores facilitadores à adesão farmacoterapêutica, bem como os dificultadores. Os fatores determinantes para o êxito à adesão, de acordo com este estudo foram: reconhecimento da depressão como doença, motivação para o tratamento/cura, interpretação positiva dos resultados, relação positiva entre médico e paciente, relação positiva entre paciente e demais componentes da equipe, suporte familiar, presença de suporte material e institucional para a valorização do tratamento e acompanhamento psicológico. Em contrapartida, os motivos pelos quais os pacientes não aderiram ao tratamento farmacológico foram: ausência do reconhecimento da depressão como uma doença, ausência da motivação para o tratamento/cura, interpretação negativa dos resultados, sintomatologia, relação negativa entre médico e paciente, relação negativa entre pacientes e os outros membros de equipe, ausência de suporte familiar, preconceito social, ausência de suporte material e institucional para viabilização do tratamento (CUNHA & GANDINI, 2009).

Em se tratando de crianças e adolescentes, o fato de os pais não compreenderem a importância do tratamento ou a gravidade da enfermidade também corrobora para a não aderência. Frente a isso, é imprescindível o desenvolvimento de um plano de tratamento da depressão em conjunção com os pais ou responsáveis, incluindo a criança ou adolescente de forma apropriada a sua compreensão. A falta de adesão pode ser reduzida a partir da oferta de uma abordagem adequada e inteligível dos princípios básicos da farmacocinética. Os motivos relatados pelos adolescentes para não aderirem ao tratamento são semelhantes aos dos adultos e estão relacionados com a doença, medicamentos, relação médico e paciente, família e o momento da adolescência (GREEN, 2008; LEITE & VASCONCELLOS, 2003; PACHECO & ARANGUIZ, 2011; OSTEBERG & BLASCHKE, 2005).

A depressão é uma enfermidade associada a baixa adesão ao tratamento farmacoterapêutico, o que pode ser explicado pelas próprias características da doença. Alguns pacientes adultos deprimidos não desejam administrar o

medicamento antidepressivo, pois creem que são capazes de conseguirem a cura sozinhos (PACHECO & ARANGUIZ, 2011).

Fato semelhante ocorre com o adolescente que possui uma maior percepção das consequências vitais da sua enfermidade, quando a sua reação emocional é mais intensa no momento do diagnóstico e a sua despreocupação acerca dos que as outras pessoas vão concluir a respeito do seu diagnóstico (PACHECO & ARANGUIZ, 2011).

A adesão irregular ao tratamento psicofarmacológico por um adolescente ou períodos sem o medicamento podem conduzir ao sofrimento deste devido a uma abstinência abrupta. Pode-se afirmar também que quanto menor a idade do paciente, menor será a sua adesão ao tratamento medicamentoso o que é agravado quando há abuso de substâncias lícitas e ilícitas. Pessoas acometidas por depressão têm maior risco de suicídio. Assim, a detecção e o tratamento adequado em pacientes com esta doença parece ser a forma mais efetiva de prevenir o suicídio (CHACHAMOVICH et al, 2009; GREEN, 1997; SHIGEMURA et al, 2010). Não cumprir ou abandonar o tratamento para depressão constitui uma preocupação importante, pois o paciente está menos propenso a atingir a remissão (MELFI et al, 1998; WARDEN et al, 2008). A principal diferença entre a prática clínica e um ensaio clínico para avaliar o tratamento é que, no contexto de um ensaio, os pacientes têm regularmente contato com a equipe de saúde que seguem os pacientes e monitoraram a adesão à medicação em estudo (EKMAN et al, 2006).

A adesão em ensaios clínicos pode ser mensurada como taxa de *dropout*, calculada por porcetagem ou número absoluto, expressando o grau de perdas durante o estudo em um dado período (MOREIRA et al, 2014). Imel & Laska (2013) entendem que taxa de *dropout* também pode ser entendida como a proporção de pacientes que iniciaram um tratamento mas não o completaram. De acordo com Abdelbaky et al (2013), há uma inconsistência conceitual na literatura a respeito de taxas de abandonos em ensaios clínicos.

Ensaios clínicos randomizados, que tiveram como intervenção medicamento antidepressivo, mostraram em seus resultados taxas de *dropout* dos participantes. Um deles, realizado por Emslie et al (2014) com 463 crianças e adolescentes, pesquisou a segurança e eficácia da duloxetina no tratamento da depressão maior e apresentou uma taxa de *dropout* de 43% dos participantes. As razões relatadas para tal fato foram: efeitos adversos, falta de eficácia, decisões dos pais para

descontinuar o tratamento, decisão do médico, decisão do patrocinador e perda no acompanhamento. Ainda, em outra pesquisa conduzida por Emslie et al (2010) com 334 adolescentes, 213 deles não seguiram no estudo, dentro os motivos elencados, encontram-se: efeitos adversos, falta de eficácia, conflito familiar, abuso de substância e falta de adesão.

No que diz respeito ao tratamento da depressão em ensaio clínicos, Machado, et al (2006) aponta que 36% dos participantes sairam do estudo. Um ponto muito importante deste estudo é a relação entre as taxas de *dropout* e os medicamentos antidepressivos utilizados. Para antidepressivos tricíclicos, houve uma taxa de *dropout* de 35.7%, enquanto que para inibidores da recaptação de serotonina (ISRS) e para inibidores da recaptação de noradrenalina (ISRN), foi de 28,4% e 2,1%, respectivamente, não havendo diferença significativa quando comparados apenas os dois últimos grupos de medicamentos. Desistências devido às reações adversas foram significativamente maiores entre aqueles que usavam antidepressivos tricíclicos e as mais citadas foram: boca seca, constipação e sudorese. Quanto à perda de eficácia não houve diferença estatisticamente significativa entre as três classes de medicamentos estudados.

Diante deste cenário, o presente trabalho pretende analisar, por meio de uma metanálise, as taxas de *dropout* de estudos do tipo ensaio clínico randomizado os quais avaliam adolescentes com depressão e que possuem intervenção medicamentosa. Ainda, pretende-se estudar os fatores relacionados que levam tais participantes a deixarem dos estudos.

2 JUSTIFICATIVA

São diversas as causas para o aparecimento da depressão na adolescência. A principal e mais grave consequência de não tratar esta doença ou não aderir ao seu tratamento, é o suicídio. A terapia farmacológica, como alternativa para cura da doença ou sua remissão, quando bem aderida e compreendida pelo paciente e família, melhora a produtividade no trabalho e na escola, predispondo o indivíduo a um desenvolvimento saudável para vida adulta. Ademais, possui papel fundamental na prevenção de recaídas e recorrências, sintomas de descontinuação do tratamento e custos financeiros adicionais e dependência de drogas (JONSSON & BEBBINGTON, 1994; MELFI et al, 1998; BRENT & BIRMAHER, 2002; HASIN et al, 2005; OMH, 2005; CRIVELATTI et al, 2007; FONTANELLA et al, 2011; MINELLI, 2011).

A taxa de *dropout* em ensaios clínicos randomizados ou a ausência de adesão ao estudo, mostram que iniciar um tratamento e não continua-lo pode limitar a sua efetividade (KILLASPY et al, 2000; MELARTIN et al, 2005). Clinicamente, pacientes que abandonam tratamento deixam de receber os benefícios da conclusão do mesmo e não se beneficiam do acompanhamento da equipe médica (SIMONS et al, 1984; EKMAN et al, 2006).

Alguns estudos de grande relevância envolvendo adolescentes e antidepressivos, no formato de metanálise, avaliaram diversos desfechos, por exemplo: uso de antidepressivos tricíclicos em crianças e adolescentes, eficácia de antidepressivos em jovens, uso de inibidores da recaptação de serotonina em adolescentes e crianças em ensaios clínicos randomizados e comportamento suicida em jovens com depressão tratados com depressão de última geração (MANEETON & SRISURAPANONT, 2000; DUBICKA et al, 2006; USALA et al, 2008; TSAPAKIS et al, 2008). Anderson & Tomenson (1995), avaliaram as taxas de descontinuação do tratamento com antidepressivos, comparando os inibidores da recaptação de serotonina e tricíclicos.

Sendo assim, um estudo de metanálise que contemple as taxas de *dropout* com adolescentes em tratamento para a depressão e que expõe os fatores relacionados à saída destes dos ensaios clínicos mostra-se importante, pois externa à comunidade científica estes dados sumarizados. Ainda, elenca os preditores ao abandono do tratamento, oportunizando conhecimento aos profissionais de sáude

envolvidos com adolescentes depressivos. Sob uma perspectiva mais ampla, auxilia na construção de programas de educação profissional, capacitando-os no âmbito de manejo e qualidade do atendimento deste tipo de paciente, promovendo a sua adesão.

3 OBJETIVOS

3.1 Objetivo Geral

Identificar as taxas *dropout* de ensaios clínicos randomizados com adolescentes deprimidos em tratamento medicamentoso para a doença e fatores associados a não adesão ao tratamento.

3.2 Objetivos Específicos

- Determinar as taxas de *dropout* em estudos associados com fármacos a algum tipo de tratamento psicológico;
- Identificar os medicamentos antidepressivos mais relacionados com alta taxas de *dropout*.
- Identificar qual faixa etária está mais relacionada ao abandono do tratamento.

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5 ARTIGO:

Dropout prevalence and associated factors in randomized clinical trials of adolescents treated for depression: systematic review and meta-analysis

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ABSTRACT

Depression currently affects 350 million people, and its prevalence among adolescents is 4-5%. Treatment with antidepressants, when properly followed, assists in healing and in the remission of symptoms, leading to improvements in various aspects of life. In the case of abandonment (dropout) of treatment or a clinical trial, the adolescent is no longer followed by the medical team. The objective was to analyze the dropout rates of randomized clinical trials of depressed adolescents receiving treatment with antidepressant drugs and the factors associated with non-adherence to treatment by summarizing this information in a systematic review and meta-analysis. Articles were retrieved from Medline, Embase, Cochrane, Clinical Trial, Psycinfo and Web of Science using the MeSH terms "depressive disorder", "randomized trials" and "adolescents". The evaluation of study quality was performed using the Cochrane Handbook for Systematic Reviews of Interventions and Jadad scales. The final sample included 50 articles, of which 44 presented dropout rates. The overall dropout prevalence was 23% (95% CI 20-27; $p < 0.0001$). With regards to age, the highest dropout prevalence was among participants over 16 years of age (33%). The group treated with serotonin norepinephrine reuptake inhibitors (SNRIs) showed higher dropout prevalence (45%), as did the intervention group that received only medication (15%). Dropout prevalence was most associated with adverse effects, followed by problems relating to clinical trials and family intervention. This study demonstrated a high dropout prevalence. The drug class with the highest dropout rate was SNRIs, although this type of drug is not indicated for adolescents. Cognitive-behavioral therapy combined with pharmacotherapy showed lower dropout prevalence. Adverse effects were the factor most associated with dropout rates, and these occur with the use of drugs with little selectivity. There was a high prevalence of dropout associated with adverse drug effects.

Keywords: adolescents, depressive disorder, dropout and antidepressant

INTRODUCTION

Depression is the leading cause of disability and the third leading cause of death among adolescents worldwide (1). It is estimated that by 2020, depression will rank first in disability adjusted life years (DALYs). The prevalence ranges from 4-8% among adolescents and 8-12% among adults (2, 3). Each year, there are more than 90,000 adolescent suicides and 4 million attempted suicides (4, 5).

There are several treatments for depression, and antidepressant drug therapy has proven effective for the treatment of symptoms (6). Adherence to treatment is critical, as it prevents relapse and suicide, improves quality of life and development and prevents the wasting of financial resources (7, 6). Complications of non-adherence to treatment can lead to the adolescent's withdrawal from social and family life, poor academic performance, changes in weight, substance abuse, risky sexual behavior, conduct problems and suicide, among other issues (8). The annual direct costs for the treatment of depression in several countries range from $ 244.09 to $ 2,488.52 per capita, and indirect costs range from $ 94.14 to $ 5,360.99. Non-adherent individuals may generate an even greater negative economic impact (9, 10).

Lack of adherence among adolescents occurs for many reasons, including the disease itself, the medication, the doctor-patient relationship, the family and the characteristics of adolescence (11, 12, 13). The desire to be accepted in certain groups and for independence and oppositional behavior are also unique to adolescence and may hinder adherence, as they are at odds with good pharmacotherapeutic compliance (14).

The difference between normal care and participating in a clinical trial is that in the latter, the medical team monitors the patient more closely, as they are following study participants for signs and symptoms as well as adherence and its causes. Dropout of any treatment type limits the effectiveness of treatment and causes damage to adolescents' health and development. Thus, it is important to identify factors associated with treatment dropout among adolescents (15, 16, 17, 18).

Several randomized clinical trials of adolescents being treated for depression have reported dropout rates, but the data were not summarized in a systematic review or meta-analysis, and the factors associated with dropout were not reported. The dropout rate quantifies the number of adolescents who abandon treatment within clinical trials, and these individuals may have been harmed. Identifying the reasons for dropout among adolescents may help to better design clinical trials and may provide health professionals with tools to

prevent non-adherence. Therefore, the present study aims to report dropout rates and factors related to dropout among adolescents treated for depression in randomized clinical trials.

METHODS

Protocol and Registration

This systematic review is in accordance with the rules of Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (19) and was duly recorded in Prospero (number CRD42014013475).

Eligibility Criteria

Studies using the following criteria were eligible for inclusion: randomized controlled trials, drug treatment for depression and depressed adolescents. Only studies published in the English language were included.

Source of Information

The studies were accessed from MEDLINE (accessed through PubMed), EMBASE, Cochrane - Central Clinical Trial Registries, ClinicalTrials.gov, Lilacs, Psycinfo and Web of Science. The cutoff date for the article search was December 2014, with no prior time criteria established. Additionally, eligible studies were screened for in the references of accessed articles and through Google Scholar.

Search

The initial search used the MeSH terms "depressive disorder", "randomized trials" and "adolescent". The strategy used with regard to the search engines is described in Table 1.

Study Selection

Initially, article titles and abstracts were independently evaluated by two expert reviewers (AR and MB) for inclusion criteria. When abstracts did not provide enough information, their articles were accessed in full. Disagreement between the expert reviewers was discussed with a third reviewer (TM).

The selected studies were evaluated with regards to the following information: year of publication, study location and time, size of the overall sample and sub-groups, average age, number of female participants, type of intervention, general dropout and dropout by sub-groups and factors associated with the dropout rate. If any of this information was not available, the authors were contacted by email to obtain the missing information. Each selected article's references and its citations in Google Scholar were also analyzed.

Evaluation of Research Quality

Article quality was evaluated based on the following criteria suggested by the Cochrane Handbook for Systematic Reviews of Interventions scale: generation of a proper sequence, investigator blinding, allocation concealment, participant blinding, evaluator blinding, blinding of outcome evaluators, intention to treat analysis and description of losses and exclusions. Each item used by the study received 1 point, and 0 points were given if it did not meet the criteria. On a scale of 0 to 8, studies with a score of 8 were classified as good; those with a score of 6 to 7 were classified as reasonable; and those scoring 5 or fewer points were considered poor (20).

The studies were also evaluated according to the Jadad scale with regard to randomization, appropriate method for generating randomization, description of blinding, appropriate blinding method and reporting of dropouts and exits. Study quality was categorized as low (< 3) and high (≥ 3) (21).

Data Extraction

Two reviewers (AR and MB) independently conducted data extraction. The collected study characteristics included the presence of a randomized clinical trial of adolescents treated for depression. The following additional information was also gathered: authors, study location, year of publication, overall sample size and sub-group size, type of intervention, general dropout rate and sub-group dropout rate and factors associated with dropout.

Analysis of Factors Associated with Dropout

Qualitative analysis was used to ascertain the factors associated with dropout, and this information was sought from every article that met the criteria. These factors were then categorized as follows: adverse effects, family intervention, issues related to the clinical trial, failure to return, inadequate response/not improved, the need for other treatment, adherence issues, symptom improvement and other reasons.

Data Analysis

A meta-analysis model for proportions was developed to evaluate the dropout rate from randomized clinical trials involving adolescents. The dropout rates and raw values were extracted from the included studies for the control and intervention groups. The heterogeneity of the studies was first examined using quantitative and qualitative criteria and clinical judgment. Quantitative factors included age group, randomized group and type of treatment received by the intervention groups. Cochrane quantitative indicators (considering *p* values of less than 0.05 for heterogeneity indicators) and H and I^2 statistics were used (22).

High I^2 values indicate high heterogeneity, with classifications of 25% (low), 45% (moderate) and 75% (high) (23). In this study, the dropout rate was considered high for several reasons; therefore, the random effects model was used for interpretation. The main objective was to summarize estimated dropout rates using a variety of studies applicable to different settings and populations.

A sensitivity analysis was conducted by including different sub-groups of studies based on the quality score of randomized clinical trials, age group, intervention or control group and types of intervention received, which allowed the robustness of the results to be tested. Study bias was evaluated using exploratory graphical analysis with funnel plots and descriptive analysis. Forest plots were drawn to describe these results. All analyses were performed using the meta package (24) and metaphor package (25) of the R software (R-Project, version 3.2.0, 2013).

To summarize the reasons associated with dropout in clinical trials, a qualitative meta-summarization was formed as an aggregation of the findings (26), and the most relevant associated factors from the included studies were grouped. This process involved summarizing the results of each included study and applying a thematic analysis. Themes based on the categorization of the associated factors were considered relevant according to the frequency and the intensity of dropout present in each evaluated study.

Effect intensities were measured according to the size of the themes. Effect intensity values were calculated by dividing the number of studies containing a particular theme (excluding any duplicates) by the total number of included studies, and this resulted in a proportion.

The adverse event intensity was calculated to indicate the following: a) which studies contributed most to identifying the most prevalent events; and b) which studies were stronger

or weaker based on their contributions to answering the research question. This was achieved by dividing the number of findings with adverse effects of > 25% contained in that study by the number of findings with adverse effects of > 25% in all studies.

This information is useful for improving the interpretation based on the quality of the meta-summarization. It also helps to determine whether some findings are derived from very weak studies, which reports have a greater frequency and thus contribute more to the findings, and which reports contain unique findings (26).

RESULTS

A total of 1,440 records were identified, of which 592 were duplicates, yielding a final count of 848 abstracts. Of these, 429 remained after the abstracts were evaluated for inclusion criteria. A total of 359 were removed because they were not randomized, leaving 70 articles. The references were then analyzed, and another 36 studies were added. Thus, a total of 104 articles were evaluated in full, and of these, 56 were excluded for being secondary analyses or for not being randomized controlled trials. The final sample included 50 articles that were used in the systematic review, of which 44 reported dropout rates (Figure 1). The characteristics of each study are presented in Table 1.

The evaluation of study quality using the Jadad scale revealed that 82% were of high quality (27-31, 33, 35-49, 51, 53, 56, 58-60, 62-68, 71-75) and 18% were of low quality (32, 34, 50, 52, 54, 55, 57, 61, 69, 70, 76) (Supplementary Table 1). No study a grade of 8, or good quality, on the Cochrane Handbook for Systematic Review scale. Twenty-four percent of the analyzed papers achieved a score of 6 or 7, i.e., reasonable quality (28, 31, 33, 37, 40, 41, 44, 45, 58, 67, 74), and 76% were of limited or poor quality (27, 29, 30, 32, 34-36, 38, 39, 42, 43, 46-57, 59-66, 68-73, 75, 76) (Supplementary Table 2).

Summary of the Results

Quantitative Analysis

The overall dropout prevalence in this meta-analysis was 23% (95% CI 20-27; $p < 0.0001$), and the random effects model showed heterogeneity (I^2) of 94.2% (Figure 2). The total sample size was 6,885 individuals. Studies showing total and per-group dropout data were included in the analyses. Due to high heterogeneity, the analysis of overall dropout was divided into two sub-analyses (intervention and control groups) to determine whether there were differences between the groups. For the group of participants randomized with regards

to the intervention, there was a dropout prevalence of 14% (95% CI 12-6; I^2 = 71.5%; p < 0.0001) (Figure 3). The dropout prevalence for the control group was 12% (95% CI 10-14; I^2 = 74.2%; p < 0.0001) (Figure 4). It is important to note that most of the studies had a control group with an active placebo, which explains the small difference between the dropout prevalences of the control and intervention groups.

Sub-analyses were also conducted to investigate whether the dropout prevalence was related to intervention type (Figure 5), age group (Figure 6) or antidepressant medication class (Figure 7).

1) Intervention Types

The sub-analysis for intervention types was divided into studies of cognitive behavioral therapy associated with antidepressant medication (CBT + med) and those of antidepressants only (med). The former had a dropout prevalence of 12% (95% CI 10-16; I^2 = 63.7%; p < 0.0001), and the latter's prevalence was 15% (95% CI 13-17; I^2 = 71.6%; p < 0.000) (Figure 5).

2) Age Group

For studies that analyzed individuals with a mean age of 10-12 years, there was a dropout prevalence of 21% (95% CI 15-31; I^2 = 53.2%; p < 0.0001). Those evaluating adolescents with a mean age of 12-14 years had a dropout prevalence of 11% (95% CI 6-19; I^2 = 95.6%; p < 0.0001). Studies with individuals with a mean age of 14-16 years had a dropout prevalence of 31% (95% CI 25-39; I^2 = 93%), and clinical trials of individuals with a mean age of 16 or over had a dropout prevalence of 33% (95% CI 27-39; p < 0.0001) (Figure 6).

3) Drug Class

This analysis was performed according to the groups of drugs used in the experimental intervention. Clinical trials that provided tricyclic antidepressants (TCAs) to their participants showed 28% dropout prevalence (95% CI 22-34; I^2 = 33.1%; p < 0.0001). For the single drug group using monoamine oxidase inhibitors (MAOIs), the dropout prevalence was 30% (95% CI 25-36). Studies using norepinephrine reuptake inhibitors had a dropout prevalence of 45% (95% CI 31-64; I^2 = 94.2%; p < 0.0001). Clinical trials with selective serotonin reuptake inhibitors showed a dropout prevalence of 21% (95% CI 17-25; I^2 = 94.1%; p < 0.0001) (Figure 7).

Qualitative Analysis

The most common reason for dropout was adverse effects, followed by issues relating to the clinical trial, family intervention, inadequate response/no improvement of symptoms, the need for other types of treatment, issues relating to adherence, other reasons and improvement of symptoms (Figure 8).

DISCUSSION

Adherence to antidepressant treatment is of utmost importance and it is rarely studied in young individuals. This meta-analysis showed a dropout prevalence of 23%, ranging from 20% to 27%, among adolescents being treated for depression. A meta-analysis about efficacy of selective serotonin reuptake inhibitors (SSRIs) among adolescents showed a dropout prevalence between 18.5% and 39.6% (77). Another study with the same design, but with a sample of undefined age, showed a dropout prevalence of 32.1% (78). There are reports that 40% of patients treated with antidepressants discontinue them in the first three months of use (79). It is understood that the optimal dropout prevalence should not exceed 20%, as a figure in excess of this number could signify dubious representativeness and reliability as well as considerable problems with regards to generalizability (80, 81). In determining the overall dropout prevalence, 2 identified articles (44, 45) showed uniquely high values. The first (44) included adolescents whose depression was resistant to conventional treatment. In this case, the high dropout prevalence can be justified by the disease itself, which makes it difficult to seek help and adhere to treatment, as such patients are shown to have cognitive impairment and a lack of energy and motivation (82). The other study, by Emslie et al (2014), showed a high rate of treatment discontinuation due to adverse events in the group treated with 60 mg of duloxetine, which is in agreement with other data in the literature (83, 84). This drug is contraindicated in children and adolescents because of a lack of evidence showing its effectiveness and efficacy (85).

The most important associated factor regarding the high rate of dropout was the adverse effects of medications. When specified, the most frequently cited symptom was mania that can occur in patients using SSRIs, MAOIs and TCAs (86). A meta-analysis showed that the risk of developing mania from antidepressants is 12.5% and that patients using TCAs have a greater chance of developing this adverse effect (87, 88). The second most mentioned adverse effect was skin rash, which may be caused by SSRIs and TCAs. The selectivity of antidepressant drugs for this reaction is not as important as the individual

patients' characteristics. Skin reaction is a rare condition and it is more common in children, young people and people over 65 years old (89). Headache was the third most prevalent adverse effect. It is considered a common reaction to SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRIs) in adolescents (90). In contrast, adolescents using bupropion are 43% less likely to have a headache than those using SSRIs. The increase of headaches can be explained by the agonist activity that fluoxetine exerts on the 5-HT_{2c} receptors (90-91).

Issues related to errors in clinical trials were also relevant with regards to the high dropout prevalence. Many studies in this meta-analysis excluded participants for protocol violations, which are understood to be avoidable mistakes that cause misinterpretation of the results (93). Loss to follow-up was also an important factor within errors in clinical trials: while loss of less than 5% of included individuals is considered acceptable, and losses higher than 20% can indicate compromised external validity of the findings (94).

Family interventions in the treatment proved to be a significant factor regarding adolescent adherence to the study, which is closely linked to caregiver/family education, income and age characteristics. Family structure is also important (single or widowed mother, number of children and families including grandparents), as is parents' mental health, family violence, substance abuse and neglect (95, 96). In addition, the interaction between dosage and family dynamics affects adherence (97). Therefore, personal or telephone contact with the doctor or team members to evaluate the understanding of the patient and family with regards to adherence and the treatment plan is critical for treatment success (95). Psychoeducational materials about depression or referrals to family therapy can also be provided during follow-up (98, 95).

Regarding treatment type, we found that the group treated with SNRIs had the highest prevalence of dropout, followed by those treated with MAOIs, TCAs and SSRIs. Only 3 studies reported the use of SNRIs (44, 45, 59). Few studies used this drug class, which reflects a global trend in treating depression in adolescents with the most indicated drugs, which are SSRIs and TCAs (99-101). A meta-analysis (102) examined 21 articles comparing dropout prevalence among individuals using SSRIs and TCAs. Dropout prevalence was higher among those using the latter drug class, which is in agreement with the data found in the present study (102). This can be explained by the fact that SSRIs are better tolerated than TCAs, as 15.9% of patients taking SSRIs experience adverse reactions compared to 22.4% of patients using TCAs (102). Patients taking SSRIs are more likely to adhere to treatment than those taking TCAs, despite sexual dysfunction and other adverse reactions being very significant among those using SSRIs (103,104). Cost is also a barrier to engaging

the patient in treatment, and in this sense, generic SSRI drug options are the most feasible (104).

Regarding intervention types, our meta-analysis found studies of drug intervention only had a higher prevalence of dropout than those offering medication and cognitive behavioral therapy in depressive adolescents. When comparing adults receiving cognitive behavioral therapy and medication simultaneously with those receiving pharmacotherapy alone, a study showed lower dropout prevalence in the former group (105). Another study that made the same comparison showed higher dropout prevalence in the group using only medication, which is in agreement with the results of the present study (105). The data therefore suggest that combination treatment is better than pharmacotherapy alone and is more effective in preventing relapse than in acute treatment as already included in clinical guideline for adults (106). Depressed patients have negative thoughts about life, feel guilty, devalue themselves, generalize failure and do not believe that problems can be solved or improved (107). In this sense, cognitive behavioral therapy works by changing patients' lifestyle, encouraging the development of skills and increasing encouragement (108). It is also indicated as an adjuvant treatment for individuals who do not respond to pharmacotherapy (105).

Regarding age, it was observed that adolescents aged 16 and older had higher dropout prevalence than younger individuals. The older the adolescent is, the greater the problems with adherence, as these individuals have acquired autonomy and have discovered that having a disease can cause impotence. This discourages them from using medications or attending consultations (95). Another important issue in adolescent dropout is the use of legal or illegal drugs during depression treatment, which makes adherence difficult because the individual may choose to take the drug rather than the prescribed antidepressant (109).

The limitations of the present study include its high heterogeneity due to the differing characteristics between trials (e.g., sample numbers and different treatment forms), which indicates that the results and conclusions should be interpreted with caution. In addition, some studies did not specify the adverse effects that predisposed participants to dropout, which hindered accurate quantification of such effects within the analysis. Some studies were removed from the sub-analyses because they did not provide the necessary data for performing calculations or the way in which the data were presented made analysis unfeasible.

CONCLUSION

The present study showed a high dropout prevalence in randomized clinical drug trials of adolescents treated for depression. The main factors associated with this high prevalence were adverse effects, problems relating to the clinical trials and family interventions. It was found that studies using SNRIs for depressive adolescents had a higher dropout prevalence while studies using SSRIs had the lowest prevalence. Another very important factor to increase treatment adherence of depressive adolescents relates to the demonstration that cognitive-behavioral therapy associated with pharmacotherapy lowers dropout prevalence

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109. Kaminer Y, Connor DF, John F, Curry JF: Comorbid Adolescent Substance Use and Major Depressive Disorders: A Review. Psychiatry, 2007; 4:32-43.

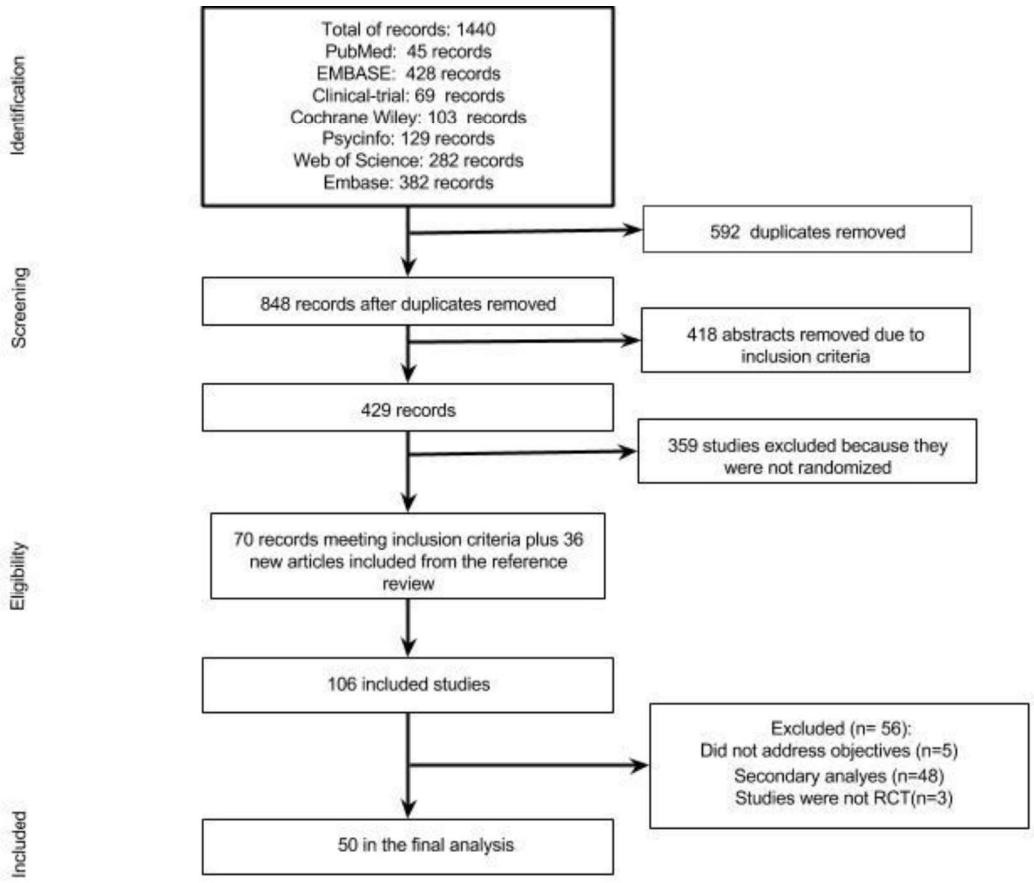

Figure 1. Flow diagram of the number of publications identified, recovered, extracted and included in the final analysis

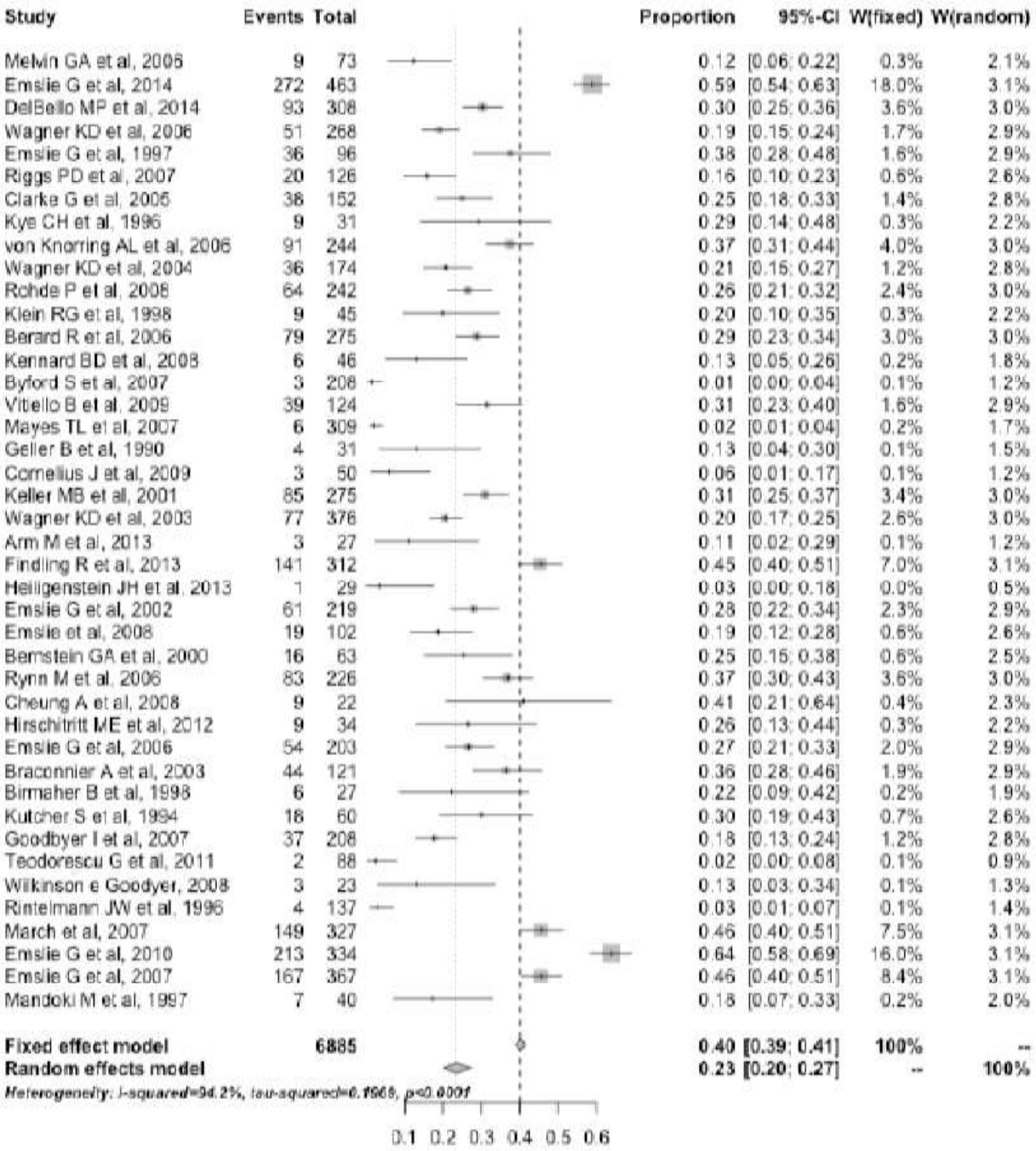

Figure 2. Overall dropout rate prevalence among selected studies.

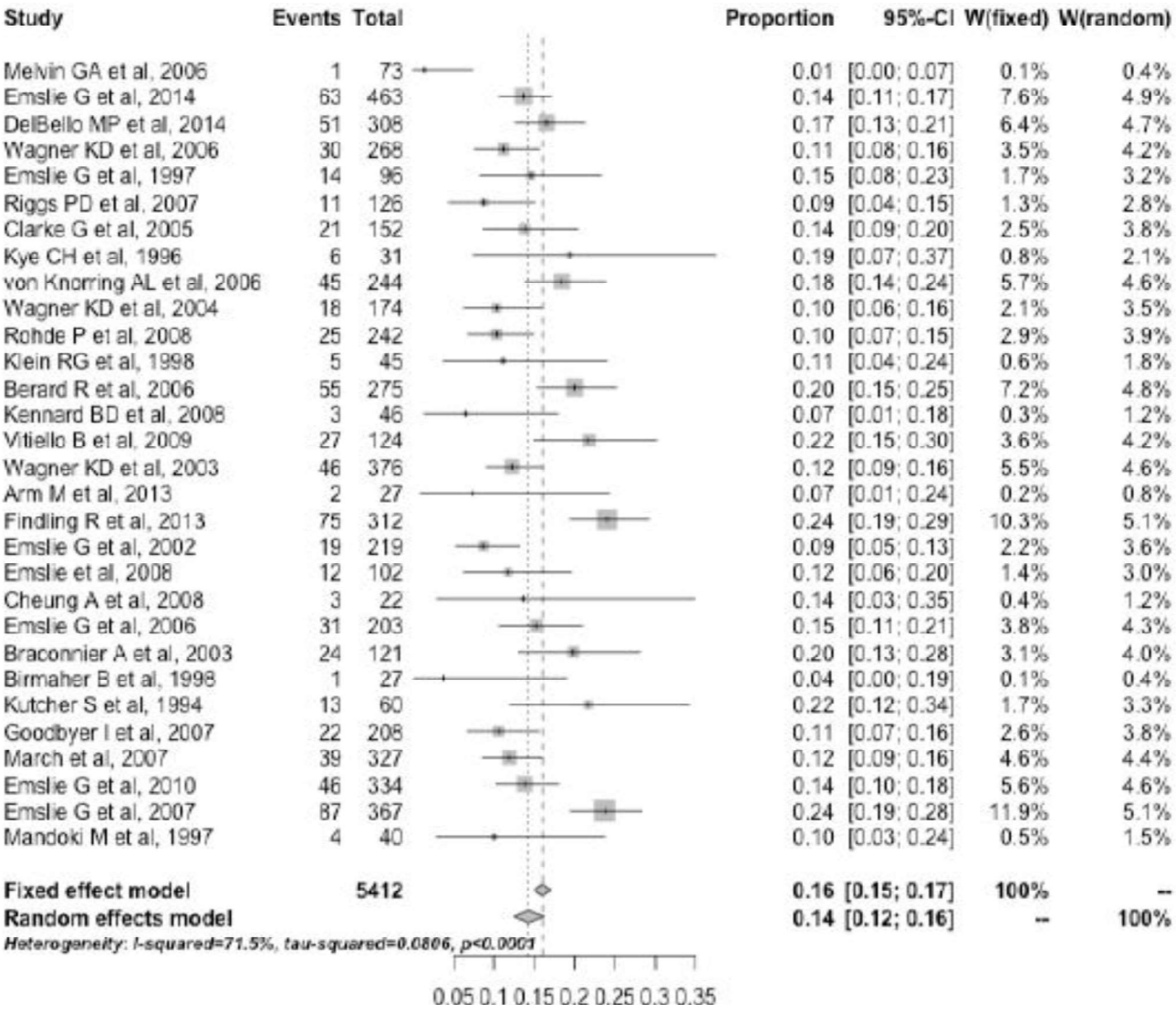

Figure 3. Dropout rate among the intervention groups.

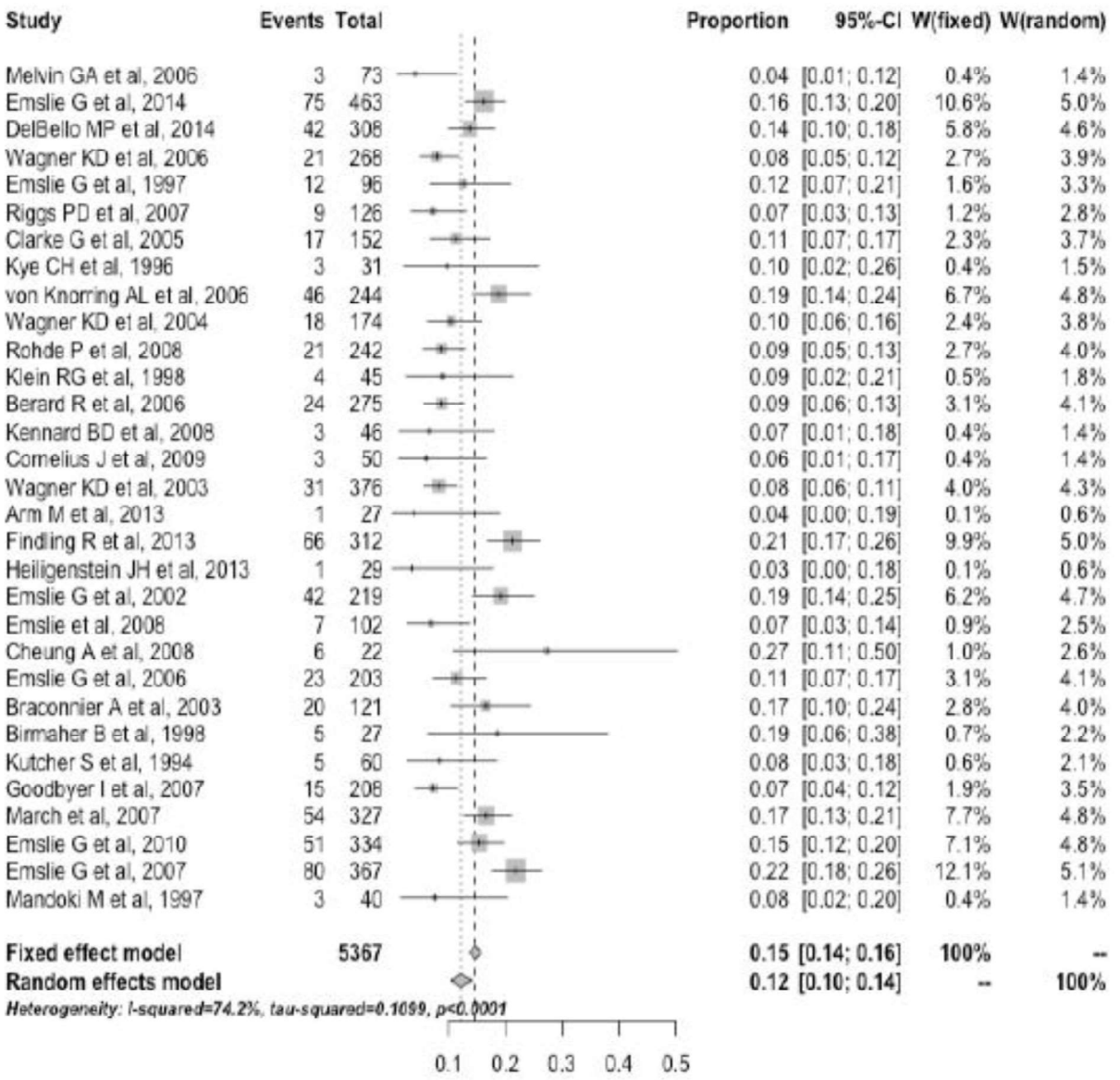

Figure 4. Dropout rate among the randomized controlled groups.

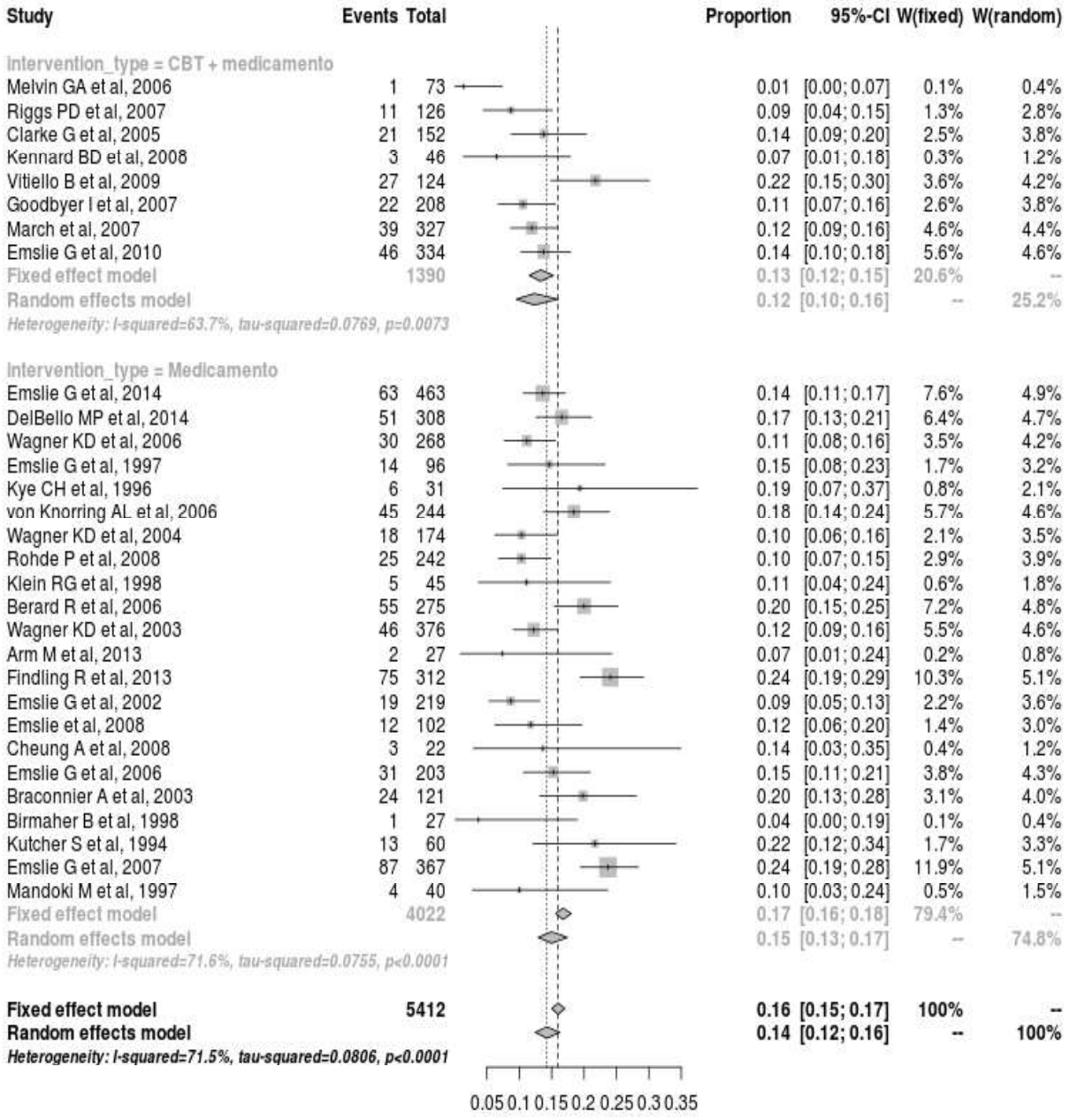

Figure 5. Dropout rate according to intervention type.

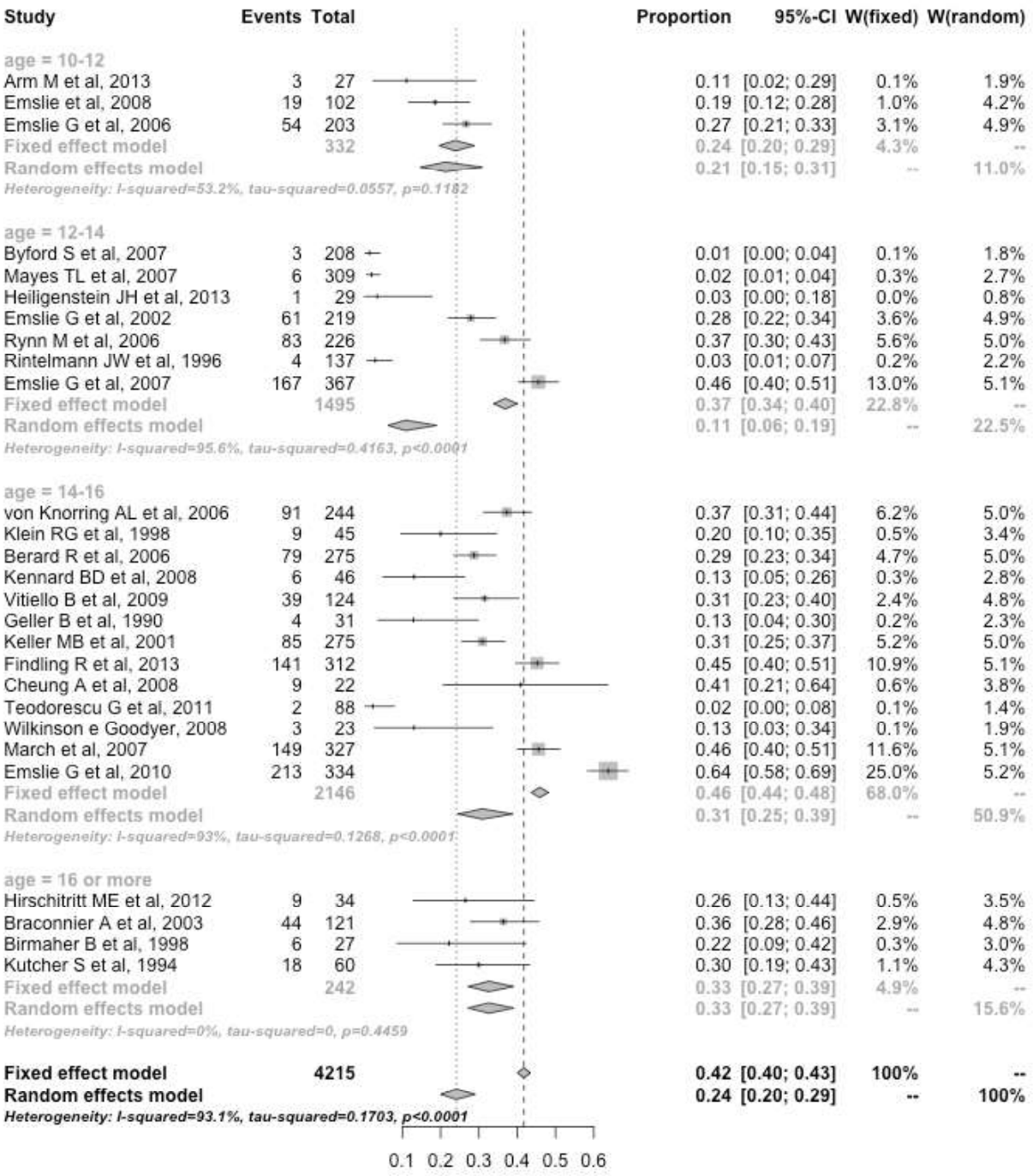

Figure 6. Dropout rate according to age group.

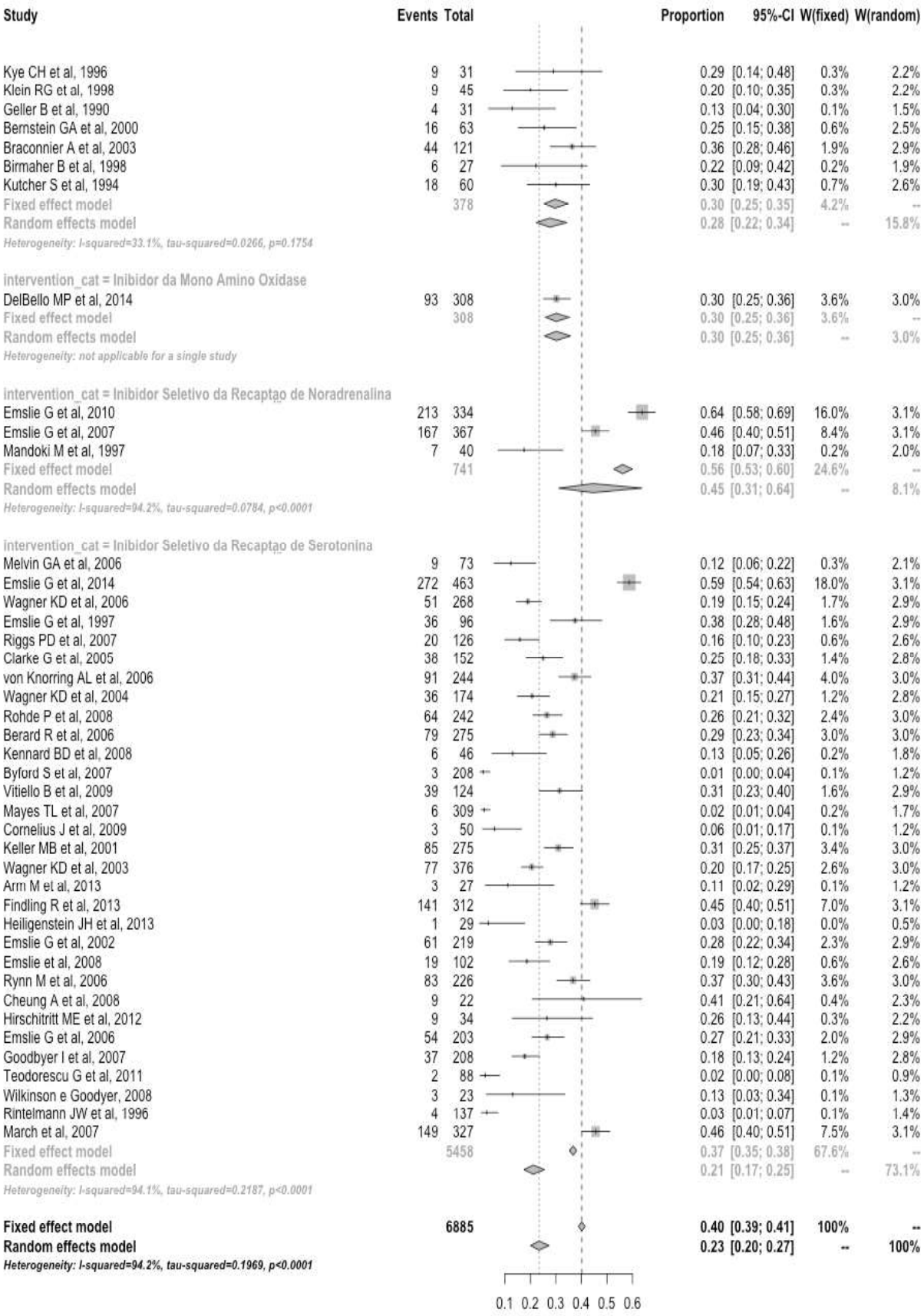

Figure 7. Dropout rate according to antidepressant medication class.

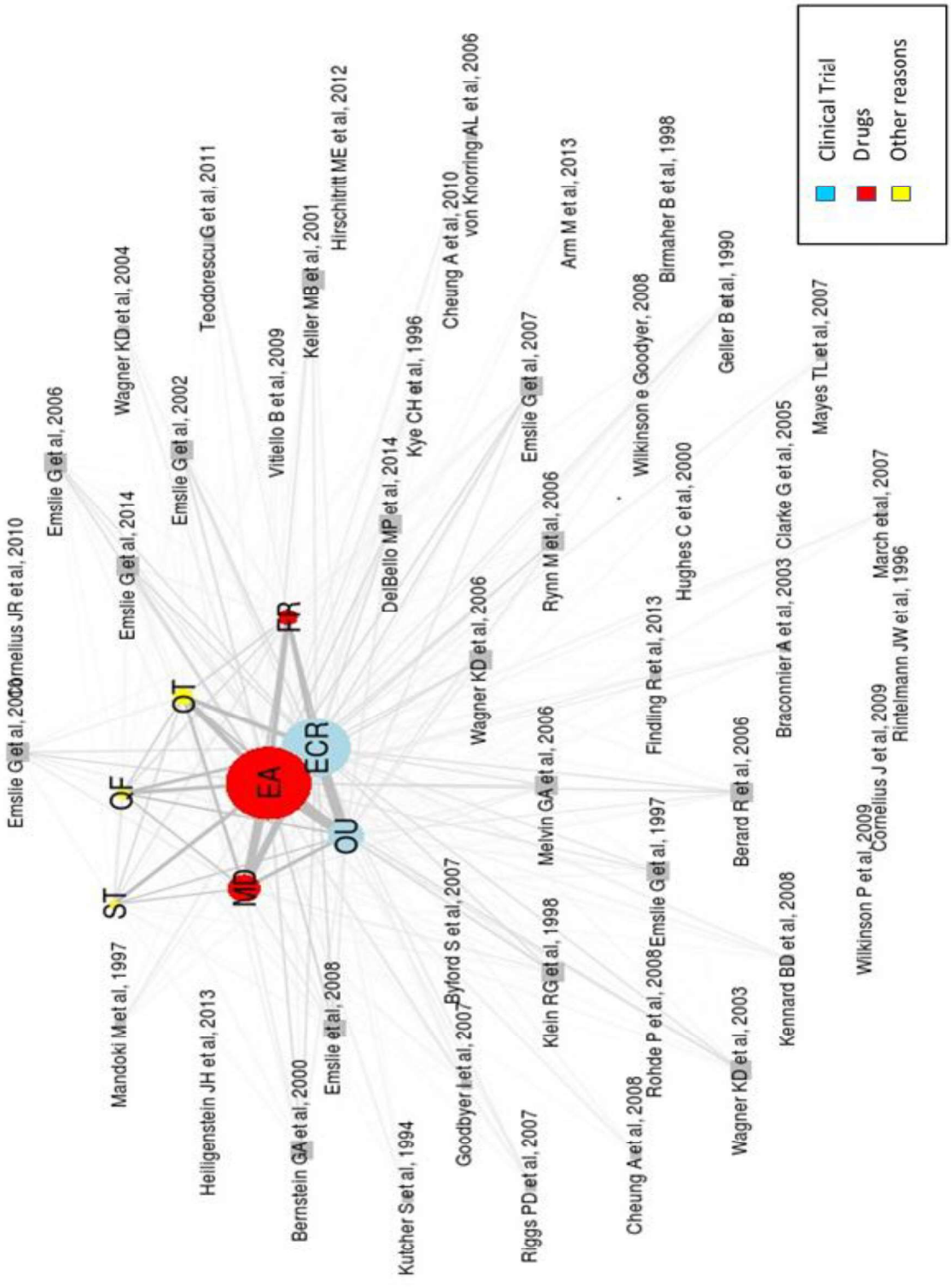

Figure 8. Association matrix of factors associated with dropout.

Table 1. General characteristics of studies found in research

Author/Year	Country	Sample Size	Intervention (experimental group; control group)	Dropout**** (experimental group; control group)	Factors associated with dropout
Amr et al (27)	Egypt	27	Vitamin C with Fluoxetine; Placebo and Fluoxetine	N/A***, 2; N/A, 1	Absence of adherence
Berard et al (28)	Belgium, Italy, Spain, UK, Holland, Canada, South Africa, Arab Emirates, Argentina and Mexico	275	Paroxetine; Placebo	N/A, 55; N/A, 24	Adverse effects, loss of efficacy, violated protocol, loss of monitoring and others
Bernstein et al (29)	United States	63	Imipramine; CBT*	10,7%, N/A; 11,4%, N/A	N/A
Birmaher et al (30)	United States	27	Amitriptiline; Placebo	N/A, 1; N/A, 5	Worsening of clinical symptoms and deviation from protocol
Braconnier et al (31)	France	121	Clomipramine; Paroxetine	41,4%, 24; 31,8%, 20	Lack of efficacy, Adverse effects, patient resistance, violation of protocol, loss of monitoring, prison
Byford et al (32)	England	208	SSRI** with CBT; SSRI	N/A; N/A	N/A
Cheung et al (33)	Canada	22	Sertraline; Placebo	N/A, 3; N/A, 6	Adverse reactions, loss of monitoring, exclusion, withdrawn consent and free re-incidence
Cheung et al (34)	United States and Canada	309	Fluoxetine; Placebo	N/A; N/A	N/A
Clarke et al (35)	United States	152	SSRI with CBT; SSRI	N/A, 21; N/A, 17	N/A
Cornelius et al (36)	United States	50	Fluoxetine; Placebo	N/A, 0; N/A, 3	N/A
Cornelius et al (37)	United States	70	Fluoxetine; Placebo	N/A, 0; N/A, 0	There was no dropout

Table 1. General characteristics of studies found in research

Author/Year	Country	Sample size	Intervention (experimental group; control group)	Dropout**** (experimental group; control group)	Factors associated with dropout
DelBello et al (38)	United States	308	Selegiline; Placebo	N/A, 51; N/A, 42	Withdrawn consent, non-adherence, protocol violation or loss of monitoring and adverse reactions
Emslie et al (39)	United States	96	Fluoxetine; Placebo	N/A, 14; N/A, 12	Adverse reactions, lack of efficacy, protocol violation
Emslie et al (40)	United States	219	Fluoxetine; Placebo	N/A, 19; N/A, 42	Adverse effects, doctor's orders, patient's decision, did not follow protocol and lack of efficacy
Emslie et al (41)	United States and Canada	203	Paroxetine; Placebo	N/A, 31; N/A, 23	Adverse effects, lack of efficacy, protocol violation, loss of monitoring and others
Emslie et al (42)	United States	367	Venlafaxine; Placebo	N/A, 87; N/A, 80	Adverse effects, did not return, refusal of patient, unsatisfactory response, protocol violation and other non-medical reasons
Emslie et al (43)	United States	102	Fluoxetine; Placebo	N/A, 12; N/A, 7	Adverse effects, withdrawn consent, loss of monitoring and non-adherence
Emslie et al (44)	United States	334	1) Venlafaxine with CBT, 2) SSRI and 3) SSRI with CBT; Venlafaxine	1) N/A, 46 2) N/A, 58 3) N/A, 58; N/A, 51	Removed from blinding, ineligible to continue, adverse effects, lack of efficacy, adjuvant treatment for other comorbidities, diverged from protocol, family conflict, substance abuse, receiving paroxetine, adherence failure and loss of monitoring.
Emslie et al (45)	United States, Canada, Mexico and Argentina	463	1) Fluoxetine and duloxetine, 2) Duloxetine and 3) Fluoxetine; Placebo	1)N/A, 63 2)N/A, 66 3)N/A, 68; N/A, 75	Adverse effects, lack of efficacy, parents' decision to discontinue, doctor's orders, sponsor's decision, loss of monitoring and abdominal pain
Findling et al (46)	United States	312	Escitalopram; Placebo	N/A, 75; N/A, 66	Unsatisfactory response, protocol violation, withdrawn consent, loss to follow-up, not complied extension criteria and adverse effects

Table 1. General characteristics of studies found in research

Author/Year	Country	Sample Size	Intervention (experimental group; control group)	Dropout**** (experimental group; control group)	Factors associated with dropout
Kennard et al (55)	United States	144	Fluoxetine with CBT; Fluoxetine	35; 44	Withdrew consent, lost to follow-up, lack of improvement, needed additional treatment, moved, non-compliance and adverse effects
Klein et al (56)	United States	45	Desipramine Placebo	N/A, 5; N/A, 4	Address change, adverse effects not related illness, improvement, compliance inappropriate
Kutcher et al (57)	Canada	60	Desipramine Placebo	N/A, 13; N/A, 5	Adverse effects and others not reported in the study
Kye et al (58)	United States	31	Tricyclic antidepressant; Placebo	N/A, 6; N/A, 3	No adherence and collateral effects
Mandoki et al (59)	United States	40	Venlafaxine; Placebo	N/A, 4; N/A, 3	Failure to attend visits and development of other mental comorbidity
March et al (60)	United States	327	Fluoxetine with CBT; Fluoxetine	N/A, 39; N/A, 54	Premature interruption, no response, left study, withdrawn consent and loss of monitoring
Mayes et al (61)	United States	309	Fluoxetine; Placebo	N/A; N/A	N/A
Melvin et al (62)	Australia	73	1) Sertraline with CBT and 2) CBT; Sertraline	1) N/A, 1; 2) N/A, 3; N/A, 3	Adverse effects, symptoms improved, patient not in region, refusal to attend
Riggs et al (63)	United States	126	Fluoxetine with CBT; Placebo with CBT	N/A, 11; N/A, 9	Did not complete study due to: detention, loss of monitoring, changed to residential treatment or moved home and removed consent
Rintelmann et al (64)	United States	137	Fluoxetine; Placebo	N/A; N/A	N/A

Table 1. General characteristics of studies found in research

Author/Year	Country	Sample Size	Intervention (experimental group; control group)	Dropout**** (experimental group; control group)	Factors associated with dropout
Rohde et al (65)	United States	242	1) Fluoxetine and 2) Fluoxetine with CBT; CBT	1) N/A, 25 2) N/A, 18; N/A, 21	Premature termination, did not respond at end of stage 1
Rynn et al (66)	United States, Canada, Costa Rica and Mexico	226	Sertraline; Placebo	N/A; N/A	Adverse reactions, investigator's decision, left study area, parents added medication or psychotherapy, refusal to continue with study medication, withdrawn consent, loss of efficacy and others
Sallee et al (67)	United States	16	Clomipramine; Saline (placebo)	0; 0	There was no dropout
Simeon et al (68)	Canada	32	Fluoxetine; Placebo	N/A, 1; N/A, 1	N/A
Teodorescu et al (69)	Romania	88	1) Sertraline with CBT 2) Sertraline; CBT	1) N/A 2) N/A; N/A	Loss of monitoring and withdrawal of consent
Vitiello et al (70)	United States	124	1) Antidepressant drug with CBT and 2) Antidepressant drug; CBT	1) N/A, 27; 2) N/A; N/A	Suicidal ideation, adherence failure, necessity of different treatment and service, withdrawal of consent and failure to return for visits
von Knorring et al (71)	Sweden	244	Citalopram; Placebo	N/A, 45; N/A, 46	Adverse effects and lack of efficacy
Wagner et al (72)	United States, Canada, Costa Rica and Mexico	376	Sertraline; Placebo	24%, 46; 17%, 31	Adverse effects, withdrawn consent, loss of monitoring, violated protocol and insufficient clinical response and others
Wagner et al (73)	United States	174	Citalopram; Placebo	N/A, 18; N/A, 18	Adverse effects
Wagner et al (74)	United States	268	Escitalopram; Placebo	N/A, 30; N/A, 21	Adverse reactions, violated protocol, withdrawal of consent, loss of monitoring, insufficient therapeutic response and other reasons

Table 1. General characteristics of studies found in research

Author/Year	Country	Sample Size	Intervention (experimental group; control group)	Dropout**** (experimental group; control group)	Factors associated with dropout
Wilkinson and Goodbyer (75)	England	23	SSRI with CBT; SSRI	N/A; N/A	N/A
Wilkinson et al (76)	England	177	SSRI with normal treatment and CBT; SSRI with normal treatment	N/A; N/A	N/A

* CBT = Cognitive behavioral therapy;
** SSRI = Selective serotonin reuptake inhibitor;
*** N/A = not applicable
**** Dropout represented as rate and absolute number

Supplementary table 1. Evaluation of study quality according to JADAD scale

First author and year of publication	Adequate sequence generation	Allocation concealment	Blinded result	Description of losses and exclusions	Analysis by intention to treat	Score
Arm et al (27)	yes	yes	yes	yes	yes	5
Berard et al (28)	yes	yes	yes	yes	yes	5
Bernstein et al (29)	yes	no	yes	yes	yes	4
Birmaher et al (30)	yes	yes	no	no	yes	3
Braconnier et al (31)	yes	yes	yes	yes	yes	5
Byford et al (32)	yes	no	no	no	no	1
Cheung et al (33)	yes	yes	yes	yes	yes	5
Cheung et al (34)	yes	no	no	no	no	1
Clarke et al (35)	yes	yes	no	no	yes	3
Cornelius et al (36)	yes	no	yes	yes	yes	4
Cornelius et al (37)	yes	yes	yes	yes	yes	5
DelBello et al (38)	yes	no	yes	yes	yes	4
Emslie et al (39)	yes	no	yes	yes	yes	4
Emslie et al (40)	yes	yes	yes	yes	yes	5
Emslie et al (41)	yes	yes	yes	yes	yes	5
Emslie et al (42)	yes	no	yes	yes	yes	4
Emslie et al (43)	yes	yes	yes	yes	yes	5
Emslie et al (44)	yes	no	yes	no	yes	3
Emslie et al (45)	yes	yes	yes	yes	yes	5
Findling et al (46)	yes	yes	yes	yes	yes	5
Geller et al (47)	yes	no	yes	yes	yes	4
Goodbyer et al (48)	yes	yes	no	no	yes	3
Heiligenstein et al (49)	yes	yes	yes	no	yes	4
Hirschitritt et al (50)	yes	no	no	no	yes	2
Hughes et al (51)	yes	no	yes	yes	no	3
Iftene et al (52)	yes	no	no	no	yes	2
Keller et al (53)	yes	yes	yes	yes	yes	5
Kennard et al (54)	yes	no	no	no	yes	2
Kennard et al (55)	Yes	No	No	No	yes	2
Klein et al (56)	yes	no	yes	yes	yes	4
Kutcher et al (57)	yes	no	no	no	yes	2
Kye et al (58)	yes	yes	yes	yes	yes	5
Mandoki et al (59)	yes	no	yes	yes	yes	4
March et al (60)	yes	no	yes	yes	no	4
Mayes et al (61)	yes	no	no	no	no	1
Melvin et al (62)	yes	yes	no	no	yes	3
Riggs et al (63)	yes	yes	no	no	yes	3
Rintelmann et a (64)	yes	no	yes	yes	yes	4
Rohde et al (65)	yes	yes	no	no	yes	3
Rynn et al (66)	yes	no	yes	yes	yes	4
Sallee et al (67)	yes	yes	yes	yes	yes	5
Simeon et al (68)	yes	no	yes	yes	yes	4
Teodorescu et al (69)	yes	no	no	no	yes	2

Supplementary table 1. Evaluation of study quality according to JADAD scale

First author and year of publication	Adequate sequence generation	Allocation concealment	Blinded result	Description of losses and exclusions	Analysis by intention to treat	Score
Vitiello et al (70)	yes	no	no	no	yes	2
von Knorring et al (71)	yes	no	yes	yes	yes	4
Wagner et al (72)	yes	yes	yes	yes	yes	5
Wagner et al (73)	yes	no	yes	yes	yes	4
Wagner et al (74)	yes	yes	yes	yes	yes	5
Wilkinson and Goodyer (75)	yes	yes	no	no	yes	3
Wilkinson et al (76)	yes	no	no	no	no	1

Yes = 1 point

No = 0 points

Supplementary table 2 – Evaluation of study quality using the *Cochrane Handbook for Systematic Reviews of Intervention*

Author/Year	Generation of a proper sequence	Allocation concealment	Blinding of investigator	Blinding of participant	Blinding of evaluators	Blinding of results evaluators	Intention to treat analysis	Description of losses and exclusions	TOTAL
Arm et al (27)	1	1	1	1	0	0	1	0	5
Berard et al (28)	1	1	1	1	0	0	1	1	6
Bernstein (29)	0	1	1	1	0	0	0	1	4
Birmaher (30)	1	0	0	1	0	0	1	1	4
Braconnier (31)	1	1	1	1	1	0	1	1	7
Byford (32)	0	0	0	0	0	0	0	0	0
Cheung (33)	1	1	1	1	1	0	1	1	7
Cheung (34)	0	0	0	1	0	0	0	0	1
Clarke (35)	0	0	0	1	1	0	1	1	4
Cornelius (36)	0	1	1	1	0	0	1	1	5
Cornelius (37)	1	1	1	1	0	0	1	1	6
DelBello (38)	0	1	1	1	0	0	1	1	5
Emslie (39)	0	1	1	1	0	0	1	1	5
Emslie (40)	1	1	1	1	0	0	1	1	6
Emslie (41)	1	1	1	1	0	0	1	1	6
Emslie (42)	0	1	1	1	0	0	1	1	5
Emslie (43)	1	1	1	1	0	0	0	1	5
Emslie (44)	1	1	1	1	1	0	1	1	7
Emslie (45)	1	1	1	1	0	0	1	1	6

Supplementary table 2 – Evaluation of study quality using the *Cochrane Handbook for Systematic Reviews of Intervention*

Author/Year	Generation of a proper sequence	Allocation concealment	Blinding of investigator	Blinding of participant	Blinding of evaluators	Blinding of results evaluators	Intention to treat analysis	Description of losses and exclusions	TOTAL
Findling (46)	1	1	1	1	0	0	1	1	5
Geller (47)	0	1	1	1	0	0	0	1	4
Goodbyer (48)	1	0	0	1	1	0	1	1	5
Heiligenstein (49)	1	0	1	1	0	0	1	1	5
Hirschitritt (50)	0	0	0	0	0	0	0	1	1
Hughes (51)	0	1	1	1	0	0	0	0	3
Iftene (52)	0	0	0	0	0	1	1	1	3
Keller (53)	1	1	1	1	0	0	0	1	5
Kennard (54)	0	0	0	0	0	0	1	1	2
Kennard (55)	0	0	0	0	0	1	1	1	3
Klein (56)	0	1	1	1	0	0	0	1	4
Kutcher (57)	0	0	0	1	0	0	0	1	2
Kye (58)	1	1	1	1	0	0	1	1	6
Mandoki (59)	0	1	1	1	0	0	0	1	4
March (60)	0	1	1	0	0	0	1	1	5
Mayes (61)	0	0	0	1	0	0	0	0	1
Melvin (62)	1	0	0	0	0	0	1	1	3
Riggs (63)	1	0	0	1	0	0	1	1	4
Rintelmann (64)	0	1	1	1	0	0	0	1	4

Supplementary table 2 – Evaluation of study quality using the *Cochrane Handbook for Systematic Reviews of Intervention*

Author/Year	Generation of a proper sequence	Allocation concealment	Blinding of investigator	Blinding of participant	Blinding of evaluators	Blinding of results evaluators	Intention to treat analysis	Description of losses and exclusions	TOTAL
Rohde (65)	0	0	0	0	1	0	0	1	2
Rynn (66)	0	1	1	1	0	0	1	1	5
Sallee (67)	1	1	1	1	0	0	1	1	6
Simeon (68)	0	1	1	1	0	0	0	1	4
Teodorescu (69)	0	0	0	0	0	0	1	1	2
Vitiello (70)	0	0	0	0	0	0	1	1	2
von Knorring (71)	0	1	1	1	0	0	1	1	5
Wagner (72)	1	1	1	1	0	0	1	1	6
Wagner (73)	0	1	1	1	0	0	1	1	5
Wagner (74)	1	1	1	1	0	0	1	1	6
Wilkinson and Goodyer (75)	1	0	0	0	0	0	1	1	3
Wilkinson (76)	0	0	0	0	0	0	0	0	0

Yes = 1 point

No = 0 point

6 ANEXOS

Guidelines for Authors on Preparing Manuscripts
General Policies

The requirements stated below are in accordance with the International Committee of Medical Journal Editors, of which *The American Journal of Psychiatry* is a member. See "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" at icmje.org.

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Manuscripts are accepted for consideration by *The American Journal of Psychiatry* with the understanding that they represent original material, have not been published previously, are not being considered for publication elsewhere, and have been approved by each author. Any form of publication other than an abstract of no more than 400 words constitutes prior publication. This includes components of symposia, proceedings, transactions, books (or chapters), invited articles, or reports of any kind, regardless of differences in readership, as well as electronic databases of a public nature. (Clinical trial registration does not constitute prior publication and will not preclude consideration for publication in the *Journal*.)

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The American Journal of Psychiatry requires, as a condition of consideration for publication, registration of clinical trials in a public trials registry. Trials must be registered at or before the onset of patient enrollment. For this purpose, a clinical trial is defined as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (for example, phase I trials), would be exempt. The *Journal* does not advocate one particular registry, but requires authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable.

An acceptable registry must include at minimum the following information: a unique identifying number, a statement of the intervention (or interventions) and comparison (or comparisons) studied, a statement of the study hypothesis, definitions of the primary and secondary outcome measures, eligibility criteria, key trial dates (registration date, anticipated or actual start date, anticipated or actual date of last follow-up, planned or actual date of closure to data entry, and date trial data considered complete), target number of subjects, funding source, and contact information for the principal investigator. To our knowledge, at present, only www.clinicaltrials.gov, sponsored by the United States National Library of Medicine, meets these requirements; there may be other registries, now or in the future, that meet all these requirements. Registration information must be provided in the cover letter at submission.

The clinical trials registration should be included at the end of the abstract. The requirement is that all clinical trials, essentially all phase 2 or later trials in which subjects are assigned to

one or more treatment arms, either pharmacological or nonpharmacological, have clinical trials registration. Authors are responsible for having obtained registration before enrolling subjects that specifies the interventions, subject numbers and type, the primary and secondary outcomes, including assessment instruments and intervals, and statistical analysis of results. If the methods and results as described in the article are not fully consistent with the clinical trials registration, then the methods should describe what differed and why, how, and when the decision was made that resulted in the difference. We recognize that other regulatory bodies, such as sponsors, institutional review boards (IRBs), and data and safety monitoring boards (DSMBs), may change trials, and this fact should be noted. If registration was not obtained prior to the start of the trial, then other evidence, such as IRB or grant documents, should be presented to the Editorial Office to document when parameters of the trial were specified. A description of this evidence should be placed in the Method section.

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All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content. The corresponding author affirms that he or she had access to all data from the study, both what is reported and what is unreported, and also that he or she had complete freedom to direct its analysis and its reporting, without influence from the sponsors. The corresponding author also affirms that there was no editorial direction or censorship from the sponsors. Preparation of drafts of manuscripts by employees of the sponsor who are not listed as authors is expressly prohibited.

Authorship credit should be based on

1) Substantial contributions to conception and design or analysis and interpretation of data.
2) Substantial contributions to drafting the article or revising it critically for important intellectual content.
3) Final approval of the version to be published.

Conditions 1, 2, and 3 must ALL be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is also not sufficient. Any part of an article critical to its main conclusions must be the responsibility of at least one author.

Only those with key responsibility for the material in the article should be listed as authors; others contributing to the work should be recognized in an Acknowledgment. (Because readers may infer endorsement of the data and conclusions, all persons acknowledged must give written permission for their contribution to be noted in print. It is the corresponding author's responsibility to obtain written permission.) Editors will require authors to justify the assignment of authorship.

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The *Journal* requires approval of manuscript submission by all authors in addition to transfer of copyright to the American Psychiatric Association so that the author(s) and the Association are protected from misuse of copyrighted material. Accepted manuscripts will not be scheduled for publication until a completed form has been received in the editorial office. It is the author's responsibility to obtain the approval of individuals before acknowledging their assistance in the paper.

In addition, authors must obtain letters of permission from publishers and pay any fees for use of extensive quotations (more than 500 words) or figures that have been previously published or submitted elsewhere.

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PATIENT ANONYMITY

Ethical and legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. Also, authors should disguise identifying information when discussing patients' characteristics and personal history.

INFORMED CONSENT

Manuscripts and letters to the Editor that report the results of experimental investigation and interviews with human subjects must include a statement that written informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained. If your submission does not contain written informed consent or Institutional Review Board approval, it will not be reviewed.

REVIEW PROCESS

All manuscripts receive an initial review by the *Journal* Editor and/or Deputy Editors to determine the originality, validity, and importance of content and conclusions. Manuscripts with insufficient priority for publication will be rejected promptly. Other manuscripts are sent for peer review. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Authors are informed about the Editor's decision after the review process is completed.

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Manuscript Submission

The American Journal of Psychiatry has implemented a web-based manuscript submission and tracking system to accelerate the peer review process and shorten the time from manuscript submission to publication decision. The *Journal* **will no longer accept manuscripts and letters by mail.**

To submit your paper, please visit the manuscript submission site at Manuscript Central and either create an account or use your existing account. Then follow the instructions to upload your manuscript. All submissions must include a title page and be accompanied by a cover letter and list of suggested reviewers.

Types of Articles

REVIEWS
Review articles are intended to bring together important information on a topic of general interest to psychiatry. This section is not intended to be a forum for the presentation of new data or meta-analyses. Review articles are usually solicited by the Editors, but we will consider unsolicited material. We rarely proceed with Review papers for which the first author is a student and has not contributed to substantive work in the field on his or her own accord. Please contact the editorial office before writing a review article for the *Journal*. The text cannot exceed 5,000 words with an abstract of no more than 250 words, a maximum of 5 tables and figures (total), and up to 50 references. Word count includes only the main body of text (i.e., not tables, figures, abstracts or references). Additional tables or figures can be submitted in a separate file as supplemental data for posting online. (See Supplemental Data for what types of data and formats are acceptable for posting online.)

ARTICLES
Articles are reports of original work that embodies scientific excellence in psychiatric medicine and advances in clinical research. Typically, articles will contain new data derived from a sizable series of patients or subjects. The text cannot exceed 3,500 words which does not include an abstract of no more than 250 words, a maximum of 5 tables and figures (total), and up to 40 references. Word count includes only the main body of text (i.e., not tables, figures, abstracts or references). Additional tables can be submitted in a separate file as supplemental data for posting online. (See Supplemental Data for what types of data and formats are acceptable for posting online.)

BRIEF REPORTS
As of May 1, 2007, the *Journal* no longer accepts brief reports for review. The percentage of brief reports meeting criteria for publication had been declining dramatically because this format did not permit definitive presentation of major research and clinical findings. Authors are encouraged to report their findings as concisely as possible in the regular article format.

OTHER SECTIONS

Editorials. Editorials are primarily solicited by the Editor, but brief commentaries (500-750 words) can be submitted for consideration.

Treatment in Psychiatry. This series highlights issues in treatment that are frequently encountered, but recognized to be difficult. An idealized brief case vignette summarizes the clinical issue. The authorship can be single or multiple, but needs to include a senior author

who has well known expertise. The author discusses the pathophysiology and psychopathology and reviews the evidence in the literature for particular treatments. The discussion should not just reiterate guidelines, but rather present the results of studies that support a therapeutic approach. The concluding paragraphs summarize what the author believes is best to do, given the available evidence and experience. Treatment in Psychiatry articles are usually solicited by the Editors, but we will consider unsolicited material. Please contact the editorial office before writing a Treatment in Psychiatry article for the *Journal*. The text should be limited to 3,500 words (no abstract) and can have up to 50 references and 1 figure.

Clinical Case Conferences. Clinical case conferences are disguised accounts of the diagnosis and treatment of actual patients who present interesting problems. A critical element is that the case should have been discussed in a departmental forum. Interesting cases seen only by individuals are more suitable for letters to the Editor. Please contact the editorial office before writing a clinical case conference for the *Journal*. The text of clinical case conferences cannot exceed 2,000 words; the submission should lead with the case (i.e., no abstract or introduction) and can have up to 20 references.

Education in Psychiatry. Articles in this series also begin with an idealized case vignette in a brief paragraph that illustrates an important problem in clinical psychiatry. The goal of these articles is to present and evaluate methods to teach students, trainees, and other psychiatrists how to treat patients with these problems. The authorship can be single or multiple, but needs to include a senior author who has well known expertise. Education in Psychiatry articles are usually solicited by the Editors, but we will consider unsolicited material. Please contact the editorial office before writing an Education in Psychiatry article for the *Journal*. The text should be limited to 2,400 words with up to 20 references and 1 figure.

Perspectives in Global Mental Health. These articles describe the practice of psychiatry worldwide. The first half of the article should describe the presentation, diagnosis, and treatment of a typical patient in a specific region or country and then the second half should highlight and discuss the unique issues—cultural, economic, political, or even military—that impact treatment in that specific country or region. In almost all countries there is a mixture of medication and culturally distinct practices, use of both should be described. Patients described can be any age. Articles should be written in a style appropriate for a worldwide audience that is interested in unique problems faced by their colleagues. Authors are welcome to use phrases in their own language but they must also be defined or translated into English. The text must be limited to 1,200 words with up to 10 references. Multiple authors are acceptable but we expect the first author to be a well-recognized physician in her or his country. Prospective authors must live and practice in the country they are describing and are encouraged to contact ajp@psych.org to inquire about whether an article about their country is or is not already in progress. Interested authors are also encouraged to send citations for one or two relevant papers that they have published in their own language or in English journals.

Images in Psychiatry. Authors may submit brief historical or contemporary snapshots of psychiatry's practitioners or other portrayals of topics of interest to psychiatrists, such as historic buildings, manuscripts, or art, with accompanying text of 250-500 words signifying their relevance to the field today. Permission for republication of images, if not the property of the submitting author, must be obtained before submission. Original unpublished or public domain images should be sought as the *Journal* does not pay permission fees for reuse.

Introspections. Brief personal vignettes of experiences that have been particularly important—moments of insight or inspiration—will be considered for publication. Introspections should be limited to 1,000 words.

Letters to the Editor. Brief letters (maximum of 500 words, including references) will be considered if they include a cover letter indicating that the correspondence is "for publication." Novel case reports and other uncontrolled observations should be submitted as Letters to the Editor. Case reports will be peer reviewed; authors must provide a list of 4 suggested reviewers and their e-mail addresses. Letters critical of an article published in the *Journal* must be received within 6 weeks of the article's publication. Letters received after the deadline will not be considered for publication; those considered will be sent to the article's corresponding author to reply on behalf of the group, which will represent the final say on the matter. No additional letters discussing an exchange published in the *Journal*'s Letters to the Editor will be considered. Such letters must include the title and author of the article and the month and year of publication. Letters that do not meet these specifications will be returned unreviewed. Letters will be published on a space-available basis.

Book Forum. Books for review should be sent to the Book Forum Editor, *American Journal of Psychiatry,* 1000 Wilson Blvd., Ste. 1825, Arlington, VA 22209. Not all books received can be reviewed. Books are received with the understanding that reviewers selected by the Editor write their independent critical appraisals of the book's content and presentation. Reprints of reviews are not available.

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Manuscript Organization and Format

All parts of the manuscript or letter to the Editor, including case reports, quotations, references, and tables, must be double-spaced throughout. The manuscript should be arranged in the following order, with each item beginning a new page: 1) cover letter, 2) title page, 3) abstract, 4) text, 5) references, and 6) tables and/or figures. All pages **must** be numbered.

COVER LETTER

The cover letters should include statements regarding Authorship, Disclosure, and Copyright Transfer. Also, it must include a list of 4 suggested reviewers and their e-mail addresses.

TITLE PAGE

Word count. The number of words in the manuscript (including abstract, text, and references) and the number of tables and figures should be noted in the upper right-hand corner of the title page. Tables and figures are no longer included in the word count.

Title. The title should be informative and as brief as possible. *Journal* style for titles is not to use declarative sentences.

Byline. See instructions for Authorship. Authors' first names are preferred over initials. Degrees should be included after each author's name.

Previous presentation. If the paper has been presented at a meeting, give the name of the meeting, the location, and the inclusive dates.

Location of work and address for reprints. Provide the department, institution, city, and state where the work was done. Include a full address for the author who is to receive correspondence and reprint requests.

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Grant support should be acknowledged in a separate paragraph and should include the full name of the granting agency and grant number.

ABSTRACT

The abstract is a single paragraph no longer than 250 words for Reviews and Overviews and Articles and no longer than 150 words for Brief Reports. All manuscripts should include structured abstracts with the following information, under the headings indicated: *Objective*—the primary purpose of the article; *Method*—data sources, subjects, design, measurements, data analysis; *Results*—key findings; and *Conclusions*— implications, future directions. If applicable, clinical trial registration information (name, number, and URL) should be listed at the end of the abstract.

TEXT

The contents of the text should include four major sections: introduction, method, results, and discussion. The method section should provide a comprehensive description of the nature of the study group, methods for recruitment, measurement and evaluation techniques (including information about reliability as appropriate), and data analysis. At the end of the section describing the study subjects, it should be clearly stated that subjects provided written informed consent after receiving a complete description of the study. Strengths and weaknesses of the study should be presented in the discussion.

Patient perspectives. As part of a new focus of presenting research in the *Journal*, authors are strongly encouraged to include as part of their submission a brief clinical vignette in which the experience of the trial is captured from the point of view of one or more subjects. These vignettes should not simply be a summary of a patient's demographic and clinical characteristics, as would be included in a case report, but rather an idea of the patient's subjective experience of participating in the study, obtained from notes or recollections of raters who performed structured clinical interviews, actual quotes from subjects, or some other mechanism. The vignettes, which should be no more than two paragraphs, will be set apart from the main body of the article in a shaded text box entitled "Patient Perspectives."

Data analysis. Adequate description of statistical analysis should be provided, including the names of the statistical tests and whether tests were one- or two-tailed. Standard deviations, rather than standard errors of the mean, are required. Statistical tests that are not well-known should be referenced. All significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For manuscripts that report on randomized clinical trials, authors should provide a flow diagram in CONSORT format and all of the information required by the CONSORT checklist. When word limits prevent the inclusion of

some of this information in the manuscript, it should be provided in a separate document submitted with the manuscript for posting online. The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org. (See Supplemental Data for what types of data and formats are acceptable for posting online.)

Abbreviations. The *Journal* is distributed to a broad psychiatric readership, therefore only a very small number of abbreviations are considered "standard" and thus acceptable for use. Spell out all abbreviations (other than those for units of measure) the first time they are used; idiosyncratic abbreviations should never be used.

Drugs. Generic rather than trade names of drugs should be used.

REFERENCES

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do not arrange the list alphabetically. References in tables and figures are numbered as though the tables and figures were part of the text. References should be restricted to closely pertinent material. Accuracy of the citation is the author's responsibility. References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text. Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in text. It is the author's responsibility to obtain permission to refer to another individual's unpublished observations. Manuscripts that are actually in press may be cited as such in the reference list; the name of the journal or publisher and location must be included. References to the editions of DSM should not be included in the reference list.

Type references in the Vancouver style shown below. Abbreviations of journal names should conform to the style used in "NLM Catalog: Journals referenced in the NCBI Databases" (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals); journals not indexed there should not be abbreviated.

1. Zinbarg RE, Barlow DH, Liebowitz M, Street L, Broadhead E, Katon W, Roy-Byrne P, Lepine J-P, Teherani M, Richards J, Brantley PJ, Kraemer H: The DSM-IV field trial for mixed anxiety-depression. Am J Psychiatry 1994; 151:1153-1162

2. Beahrs JO: The cultural impact of psychiatry: the question of regressive effects, in American Psychiatry After World War II: 1944-1994. Edited by Menninger RW, Nemiah JC. Washington, DC, American Psychiatric Press, 2000, pp 321-342

3. Burrows GD, Norman TR, Judd FK, Marriott PF: Short-acting versus long-acting benzodiazepines: discontinuation effects in panic disorders. J Psychiatr Res 1990; 24(suppl 2):65-72

TABLES

The *Journal* does not publish tables that have been submitted elsewhere or previously published. Tables that duplicate material contained elsewhere in the manuscript (in text, figures, or other tables) will not be used. Authors should delete tables containing data that could be given succinctly in text. A copy of each table must be submitted with the manuscript and must be accessible for copyediting. Tables cannot be embedded within the document or provided as figure art. Authors providing tables in such a manner will be required to resubmit tables in a format that allows for copyediting. In terms of data presentation, values expressed

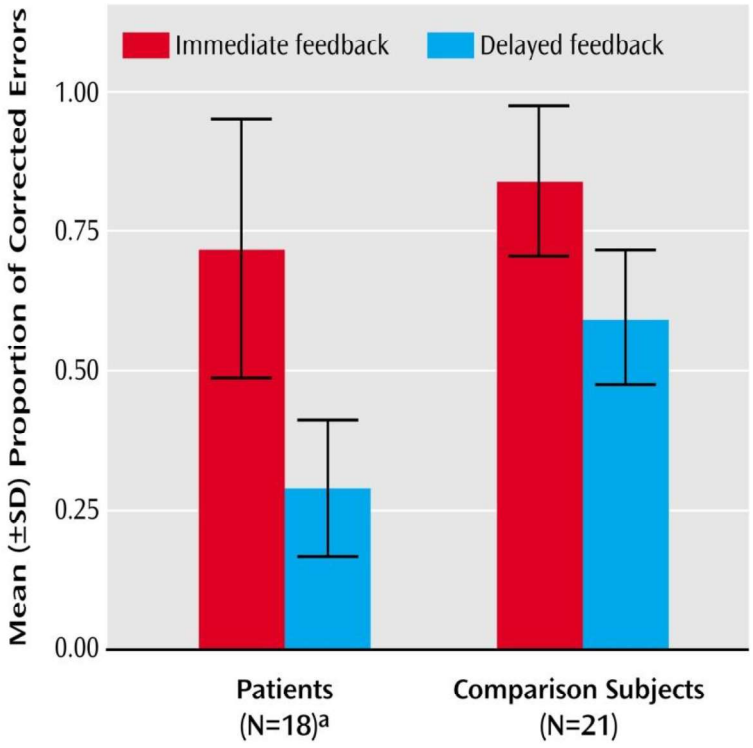
in the same unit of measurement should read down, not across; when percentages are presented, the appropriate numbers must also be given. In preparing the tables, each cell should contain only one item of data. In rows, subcategories should be in separate cells; in columns, Ns and %s or Means and SDs should be in separate cells. For optimum readability and presentation, tables should not exceed 120 characters in width. For other guidelines, consult recent issues of the Journal.

FIGURES

As part of a new focus of presenting research in the *Journal*, all authors are encouraged to include as part of their submission a figure that summarizes the major findings of the study. The *Journal* encourages the submission of high-quality color figures (previously published figures are discouraged). Multiple figures for the same article should be prepared as a set, consistent in color and size across all figures.

Consult recent issues of the *Journal* and the following guidelines for format. A copy of each figure should be submitted with the manuscript. If accepted, figures in manuscripts should be sent as high-resolution .eps or .tif files.

FIGURE 1. Neuropsychological Performance of Patients With Schizophrenia and Healthy Comparison Subjects



[a] Significant difference between test conditions (t=2.45, df=37, p= 0.02).

Submission

1. A copy of each figure must accompany the manuscript.
2. Figure titles and footnotes should be provided within the text of the manuscript.

3. If figures have been previously adapted from an earlier publication, the author must secure written permission from the holder of copyright for use in the Journal. The author should submit a copy of the permission release and credit lines if the manuscript is accepted for publication.

Format

1. Definitions of symbols appearing in the figure should be presented in a key within the figure, rather than in the title or footnotes.

2. Except for the key, avoid using internal type (e.g., placing statistical values within a graph).

3. Two-dimensional graphs should not be represented in three dimensions.

Content

1. Each complete figure (including titles and footnotes) should be understandable without reference to the text.

2. Figures should represent data visually rather than numerically.

3. If error bars are included, standard deviations, rather than standard errors of the mean, should be used.

4. Only the most widely recognized abbreviations may be used.

5. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.

6. Ordinary footnotes should be cited with lower-case superscript letters. Footnote citations may be given in both the title and the body of the figure; within the body of the figure, they should proceed from left to right.

7. For statistical comparisons noted in figures, provide complete statistical data in footnotes (see example). If numerous analyses are presented, simple p values may be given in the footnotes, in which case the footnotes should be indicated by single asterisk, double asterisk, etc.

SUPPLEMENTAL DATA

The *Journal* now allows authors to submit supplemental data to be posted online in support of their printed articles. To be accepted for posting, supplemental material must be essential to the scientific integrity and excellence of the manuscript. The material is subject to the same editorial standards as the printed *Journal* and will be submitted for peer review. Supplemental material will not be formatted or edited by in-house editorial staff to the extent as performed for material appearing in the print version. The Editor may select material submitted for publication in the print version to be posted online only. The *Journal* will accept the following categories of supplemental data:

- Detailed tables (up to 3) that contain data of use to other investigators. Data should be summarized in the text of the print version

- The CONSORT table and figure for clinical trials are also appropriate for online publication only.

- Appendices. Questionnaires, tests, checklists, etc., should be submitted as supplemental data.

Supplemental data should be uploaded in a separate file from the for-print manuscript. Please remember that the larger the file size the longer it will take users to download. For this reason, please limit your files to 10 MB. The Journal can accept the following formats:

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- JPEG image (.jpg)
- GIF image (.gif)
- Adobe PDF (.pdf)
- Excel spreadsheet (.xls)
- ZIP compressed file (.zip)
- Word document (.doc)
- Tiff image (.tif)
- PowerPoint presentation (.ppt)
- Encapsulated Postscript document (.eps)
- Mp3 file (.mp3)
- QuickTime video

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Processing of Accepted Manuscripts

Manuscripts are accepted with the understanding that the Editor and the editorial staff have the right to make revisions aimed at greater conciseness, clarity, and conformity with Journal style. Preliminary page proofs will be sent to the corresponding author. Authors who will be away from their offices for a long period or who change address after notification of acceptance should inform the *Journal* staff.

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