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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS: BIOQUÍMICA

NOVOS USOS PARA MEDICAÇÕES PSICOTRÓPICAS CONHECIDAS

LUÍSA WEBER BISOL

Prof. Dr. Diogo Rizzato Lara
Orientador

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Autora: Luísa Weber Bisol

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SUMÁRIO

RESUMO

O objetivo desta tese de doutorado foi testar psicofármacos tradicionais em aplicações diferentes das originais, tendo por base o conhecimento de seus mecanismos de ação e uma visão clínica focada no temperamento. A primeira parte da tese é constituída pelo ensaio clínico de flunarizina comparado com haloperidol no tratamento de pacientes com esquizofrenia. A segunda parte é composta de três relatos de caso oriundos da prática clínica e que, apesar de freqüentes, não costumam ser objetos de pesquisa. A flunarizina, um bloqueador de canal de cálcio empregado para tratar enxaqueca e vertigem foi escolhida pelo fato dela produzir sinais e sintomas extrapiramidais em pacientes idosos, o que posteriormente foi relacionado a sua propriedade como antagonista dos receptores dopaminérgicos do tipo D2, além da existência de dados em modelos animais que indicavam o seu potencial efeito antipsicótico. A flunarizina foi eficaz como antipsicótico e apresentou um perfil de efeitos adversos favorável, além de ter uma meia-vida longa e baixo custo. A segunda parte da tese apresenta relatos de casos clínicos freqüentes, mas pouco estudados no âmbito científico. Nesse sentido propomos uma avaliação do paciente com base no temperamento afetivo e emocional, de acordo com o modelo de temperamento proposto por Lara e Akiskal (2006). O primeiro aborda o uso de baixas doses de risperidona no tratamento de ciúme patológico. O segundo se refere à comorbidade do transtorno obsessivo-compulsivo e transtorno bipolar, tratados com divalproato de sódio e lamotrigina. O último artigo aponta para o uso de baixas doses de quetiapina em pacientes com sintomas sublimiares e temperamento hipertímico ou ciclotímico que apresentam desregulação emocional. Em conjunto, nossos resultados reforçam a idéia de que as medicações existentes podem sem mais exploradas para o tratamento de quadros clínicos diferentes das suas indicações originais.

Palavras-Chave: Flunarizina e esquizofrenia. Risperidona. Divalproato de sódio. Lamotrigina. Quetiapina.

ABSTRACT

The aim of this thesis was to test traditional drugs in applications different from the original, on the basis the knowledge of the mechanisms of action and a vision clinic focused on temperament. The first part of thesis consists in clinical trial of flunarizine compared with haloperidol in the treatment of patients with schizophrenia. The second part is composed by three case reports from clinical practice and that, despite frequent, not usually are objects of research. Flunarizine, a calcium channel blocker used to treat migraine and vertigo, was chosen because it induces extrapyramidal signs in elder patients which was later related to antagonist properties at dopamine D2 receptors, beyond the existence of data in animal models, which indicated its potential antipsychotic effect. Flunarizine was effective as antipsychotic and it presents a favorable side effects profile, beyond the long half-life and low cost. The second part of the thesis presents reports of frequent cases, but little studied under scientific scope. Therefore, we propose an evaluation of the patient with basis on the affective and emotional temperament, according to the temperament model proposed by Lara and Akiskal (2006). The first deals with the use of low doses of risperidone in the treatment of pathological jealousy. The second refers to the comorbidity of obsessive-compulsive disorder and bipolar disorder, treated with divalproex sodium and lamotrigine. The last article points to the use of low doses of quetiapine in patients with subthreshold symptoms and hyperthymic or cyclothymic temperaments presenting emotional deregulation. Together, our results strengthen the idea that the existing medications can be further explored for the treatment of clinical indications different from their originals.
Key-words: Flunarizine and schizophrenia. Risperidone. Divalproex, Quetiapine.

LISTA DE ABREVIATURAS

CID 10 – Classificação Internacional de Doenças – 10ª. edição

DSM IV-TR – Diagnostic and Statistical Manual of Mental Disorders – 4 ed. Texto Revisado

D_1 – receptor de dopamina tipo 1

D_2 – receptor de dopamina tipo 2

D_3 _ receptor de dopamina tipo 3

EEG – eletroencefalograma

GABA – ácido γ-aminobutírico

5-HT – 5-hidroxitriptamina (serotonina)

5-HT_{2A} – receptor de serotonina tipo 2A

5-HT_{1A} – receptor de serotonina tipo 1A

5-HIAA – ácido 5-hidroxi-3-indol acético

H1 – receptor de histamina H1

[^{3}H]-BTX-B – 3H-batracotoxina-A 20-alpha-benzoato

LCR – líquido céfalo-raquidiano

MK-801 – (+)-10,11-dihidro-5-metil-5H-dibenzo[a,d]ciclohepteno-5,10 imina

NGF – fator de crescimento neuronal

NMDA – N-metil-D-aspartato

P 50 – potencial evocado P 50

PCP – fenciclidina

SEP – sintoma extrapiramidal

INTRODUÇÃO

Os psicofármacos em geral recebem denominações com origem no nome do primeiro transtorno mental ou grupo de sintomas em que determinada droga foi terapeuticamente eficaz. Tais denominações podem ser concebidas como artificialidades que acompanham as atuais classificações dos transtornos mentais DSM-IV TR (Diagnostic and Statistical Manual of Mental Disorders – 4ª. Edição, Texto Revisado) e CID-10 (Classificação Internacional de Doenças – 10ª. Edição) (LECRUBIER, 2008).

Do ponto de vista clínico, muitas vezes há dificuldade de convencer um paciente que não está psicótico a usar uma medicação chamada de antipsicótico para outra indicação, um paciente com transtorno de humor a usar um anticonvulsivante ou um paciente com fobia social a usar um antidepressivo (LARA E SOUZA, 2001).

Alternativas para o tratamento farmacológico dos transtornos mentais e de outros quadros clínicos não contemplados nas classificações vigentes são importantes na realidade clínica. Essas opções podem compreender novos usos para medicações não psiquiátricas, usos e posologias diferenciados para psicofármacos amplamente utilizados e pesquisa de novas drogas. Particularmente em nosso país, a busca de medicações eficazes, bem toleradas e de custo acessível é uma questão de grande importância.

Dentro dos referenciais da "Medicina baseada em Evidências", relatos de caso são considerados evidências mais frágeis e inferiores. No entanto, esses relatos podem confirmar, modificar e questionar teorias existentes, além de indicar novos caminhos (FARMER, 1999). Historicamente as observações isoladas de poucos casos auxiliaram no desenvolvimento de novos

agentes farmacológicos, como por exemplo, as ações psicotrópicas das drogas clorpromazina e imipramina, e mais recentemente a descoberta do sildenafil no tratamento da disfunção erétil.

Essa tese aborda o novo uso de psicofármacos nas seguintes situações:

(1) flunarizina no tratamento da esquizofrenia;

(2) risperidona no ciúme patológico; lamotrigina e divalproato no tratamento do transtorno obssessivo-compulsivo e quetiapina em dose baixa em pacientes do espectro bipolar.

No primeiro capítulo estabelecemos o novo uso do psicofármaco flunarizina como antipsicótico e não questionamos a validade do diagnóstico de esquizofrenia. No segundo capítulo discutimos uma nova abordagem diagnóstica com base no temperamento que permite inferir sobre novas aplicações de psicofármacos e apresentamos relatos de casos que sugerem que essas inferências têm aplicabilidade clínica.

PARTE I – ESQUIZOFRENIA

I.1 Epidemiologia e Diagnóstico

A esquizofrenia é uma grave síndrome neuropsiquiátrica que envolve principalmente cognição, emoção e percepção. A prevalência é de cerca de 1% da população mundial (entre 0,6 e 1,5%) e causa prejuízos significativos e duradouros (SAHA et al., 2005; PERÄLÄ et al., 2007).

Os sintomas surgem caracteristicamente entre os 15 e 30 anos. A incidência é discretamente maior entre os homens (razão homens/mulheres = 1,4) (MCGRATH, 2005), sendo que em mulheres os sintomas tendem a se manifestar, em média 5 anos mais tarde. Nas mulheres há um segundo pico de incidência na peri-menopausa (HÄFNER et al., 1998). Migrantes e residentes em áreas urbanas têm maior incidência de esquizofrenia (MCGRATH, 2005). O risco de desenvolvimento de esquizofrenia é maior quando existe história familiar da doença, especialmente se há parentesco de primeiro grau ou mais de um membro da família afetado (KENDLER, 2000).

O diagnóstico de esquizofrenia é baseado em características clínicas, incluindo sintomas, curso e exclusão de outros diagnósticos médicos. Os critérios foram operacionalizados para uso em pesquisa e clínica pela Associação Psiquiátrica Americana (DSM-IV TR) (Tabela 1) e pela Organização Mundial da Saúde (CID-10).

Os sintomas são agrupados em categorias: sintomas positivos, negativos e de desorganização. Os sintomas positivos são características que os pacientes têm a mais quando comparados a indivíduos saudáveis e incluem os delírios e alucinações. Os delírios são alterações do pensamento, idéias infundadas, irreais e culturalmente não aceitas nas quais o

paciente acredita com convicção. Os delírios mais comuns em esquizofrenia são de cunho persecutório ou de referência, e podem apresentar características bizarras. As alucinações são alterações da sensopercepção que podem envolver um ou mais órgãos dos sentidos. As alucinações mais frequentes são as alucinações auditivas, que podem ser vozes (várias ou uma voz apenas) falando com ou fazendo comentários sobre o paciente.

Os sintomas negativos são características normais que faltam aos pacientes esquizofrênicos e incluem sintomas como embotamento afetivo (hipomodulação do afeto), avolição (falta de vontade e iniciativa), anedonia (falta de prazer), alogia (discurso empobrecido), apatia e isolamento social.

Os sintomas de desorganização incluem comportamento estranho ou bizarro, pensamento desorganizado, por vezes desagregado e afeto inapropriado. Além desses sintomas, os pacientes em geral apresentam déficits cognitivos que incluem prejuízos na atenção, memória de trabalho, aprendizado, fluência verbal e função executiva.

Os critérios diagnósticos de acordo com o DSM-IV TR são apresentados na Tabela 1.

Tabela 1: Critérios diagnósticos segundo DSM-IV TR

Critérios A: Sintomas característicos: dois (ou mais) dos seguintes, cada qual presente persistentemente durante um mês (ou menos se tratado com sucesso):

1. delírios;
2. alucinações;
3. desorganização da fala (p.ex.: interrupção freqüente ou incoerência);
4. comportamento grosseiramente desorganizado ou catatônico;
5. sintomas negativos i.e. embotamento afetivo, alogia ou avolição.

Nota: apenas um sintoma do critério A é necessário se os delírios forem bizarros ou se as alucinações consistirem em uma voz mantendo comentários contínuos sobre comportamento ou pensamentos da pessoa, ou duas ou mais vozes conversando entre si.

Critérios B: Disfunção Social/ Ocupacional: Por um período de tempo significativo desde o início do distúrbio uma ou mais áreas de atividade, tais como, o trabalho, relações interpessoais ou cuidados pessoais, estão acentuadamente abaixo do nível alcançado antes do início da doença (ou quando o início for na infância ou adolescência, incapacidade de atingir o nível esperado de alcance interpessoal, acadêmico ou ocupacional).

Critérios C: Duração: Sinais contínuos de disfunção persistem por pelo menos seis meses. Esse período de seis meses deve incluir pelo menos um mês de sintomas característicos (ou menos, se tratado com sucesso) e pode incluir períodos de sintomas prodrômicos e residuais. Durante esses períodos prodrômicos ou residuais os sintomas podem manifestar-se apenas por sintomas negativos ou sintomas do Critério A presentes de forma atenuada (por exemplo: crenças estranhas, experiências perceptivas inusitadas).

Critérios D: Exclusão de Transtorno de Humor ou Esquizoafetivo.

Critérios E: Exclusão do Uso de Substâncias/ Condição Médica Geral: o distúrbio não se deve a efeitos fisiológicos diretos de uma substância (por exemplo: drogas ilícitas, medicação), ou uma condição médica geral.

I.2 Neuroquímica da Esquizofrenia

Evidências sugerem que a esquizofrenia é um transtorno sutil do desenvolvimento e da plasticidade cerebrais. Alterações na migração neuronal, sinaptogênese e "poda" neuronal são associadas ao desenvolvimento posterior da esquizofrenia (MIYAMOTO et al., 2003).

As primeiras hipóteses neuroquímicas sobre a esquizofrenia estão relacionadas ao mecanismo de ação dos antipsicóticos e à indução de sintomas psicóticos por agonistas dopaminérgicos (anfetamina). De acordo com a hipótese dopaminérgica, os sintomas positivos da esquizofrenia são decorrentes de hiperatividade da transmissão dopaminérgica nos receptores D_2 nas via mesolímbica e os sintomas negativos são conseqüência de um déficit de atividade da via dopaminérgica mesocortical (ROSS et al., 2006).

Outras hipóteses neuroquímicas envolvem os sistemas glutamatérgico, serotoninérgico e adenosinérgico (MIYAMOTO et al., 2003; LARA e SOUZA, 2000). Os principais achados neuroquímicos da esquizofrenia estão sumarizados no quadro abaixo.

Tabela 2 – Alterações neuroquímicas da esquizofrenia

Neurotransmissor	
Dopamina	**↑ receptores D_2 estriado** **↑ conteúdo ou metabolismo de dopamina** **↑ transmissão dopaminérgica estimulada por anfetamina** **↓ receptores D_1 corticais** **↑ receptores D_3 corticais**
Serotonina	**↓ receptores 5-HT_{2A} corticais** **↑ receptores 5-HT_{1A} corticais** **concentrações de 5-HIAA no LCR relacionadas aos sintomas negativos**
Glutamato	**↓ expressão de receptores não-NMDA no córtex temporal e hipocampo** **↑ expressão cortical de subunidades de receptores NMDA** **↑ recaptação de glutamato no córtex frontal** **↓ liberação cortical de glutamato**

(Adaptado de MYAMOTO et al, 2003)

I.3 Tratamento da Esquizofrenia: antipsicóticos de primeira e segunda geração

A introdução do primeiro antipsicótico, a clorpromazina, na década de 1950 causou uma revolução no manejo da esquizofrenia e de outros transtornos psicóticos. Essa descoberta foi um grande avanço terapêutico e auxiliou a compreensão das bases neuroquímicas da esquizofrenia bem como a pesquisa de outros fármacos, como o haloperidol. Logo após o uso dessas medicações ter se expandido, observou-se a indução de efeitos adversos extrapiramidais (parkinsonismo, acatisia, distonia, discinesia tardia). Esses parâmetros motores serviram de base para a descoberta de novos antipsicóticos.

Na década de 1970 foi descoberta a clozapina, o primeiro antipsicótico de segunda geração (atípico) que não induz sintomas extrapiramidais (SEP). No final da década de 1970, essa medicação foi retirada de mercado de vários países devido ao risco de agranulocitose e somente em 1988 foi reintroduzida em função da sua eficácia diferenciada em quadros refratários a outros antipsicóticos (KANE et al., 1988).

Depois da clozapina, outros antipsicóticos de segunda geração foram sintetizados e demonstraram eficácia no tratamento da esquizofrenia, como amisulprida, risperidona, olanzapina, quetiapina, ziprazidona, aripiprazol e paliperidona (BREIER et al., 2005; SIMPSON et al., 2005; HIRSCH et al., 2002; KANE et al., 2002). Esses antipsicóticos são classificados como atípicos pelas características de: (1) risco reduzido de induzir efeitos extrapiramidais; (2) aumento menor e/ou transitório de prolactina (com exceção de amisulprida e risperidona); (3) eficácia em sintomas positivos, negativos e cognitivos; (4) mecanismo de ação que envolve dopamina e serotonina e/ou especificidade sobre neurônios do sistema mesolímbico sobre o estriatal; (5) eficácia no tratamento de esquizofrenia resistente, sendo esse critério bem mais aplicável à clozapina do que aos demais antipsicóticos de segunda geração (FARAH, 2005).

Essas medicações foram inicialmente propostas como um grande avanço. Entretanto, apesar da baixa indução de SEP, algumas delas podem acarretar ganho de peso e alterações metabólicas importantes (síndrome metabólica) (KELTNER, 2006).

Lieberman et al. (2005) conduziram um grande estudo (Clinical Antipsychotic Trials of Intervention Effectiveness – CATIE) comparando os antipsicóticos de segunda geração e o antipsicótico de primeira geração perfenazina. Foram incluídos 1493 pacientes com esquizofrenia de 57 centros que foram randomizados para receber risperidona, olanzapina, quetiapina, ziprazidona e perfenazina em um ensaio duplo-cego de 18 meses. O objetivo principal foi avaliar diferença na efetividade dos cinco psicofármacos. O tempo para interrupção do tratamento por qualquer causa foi maior no braço olanzapina, mas a diferença não foi estatisticamente significativa. Também não houve diferença significativa entre os grupos nos parâmetros tempo para interrupção por falta de eficácia e por efeitos adversos intoleráveis. Esses resultados colocaram em cheque a superioridade dos antipsicóticos atípicos em relação aos típicos.

Kahn et al. (2008) realizaram em estudo clínico, randomizado e aberto comparando antipsicóticos de segunda geração com doses baixas do antipsicótico de primeira geração haloperidol, com seguimento de um ano. Foram incluídos 498 pacientes de 50 centros que foram randomizados para receber haloperidol, amisulprida, olanzapina, quetiapina ou ziprazidona. O número de pacientes que descontinuaram o tratamento por qualquer causa foi maior no grupo que recebeu haloperidol quando comparado com os antipsicóticos de segunda geração, embora a redução de sintomas tenha sido praticamente a mesma em todos os grupos.

I.4. Flunarizina

A difenilpiperazina flunarizina e seu composto relacionado cinarizina são conhecidas pela capacidade de inibir canais de cálcio, especialmente os do tipo T (TODD e BENFIELD, 1989). Essas drogas têm sido usadas para o tratamento de enxaqueca, cefaléia em salvas, vertigem, hemiplegia alternante da infância, ataxia cerebelar progressiva, epilepsia e déficits cognitivos relacionados a distúrbios cerebrovasculares (TODD e BENFIELD, 1989; LEONE et al., 1991; ASTARLOA et al., 1989; NEVILLE e NINAN, 2007; MARTI et al., 2008; SCHMIDT e OESTREICH, 1991). A maior diferença entre elas é a meia-vida de eliminação, que é de cerca de 3 horas para a cinarizina e de 2 a 7 semanas para a flunarizina (KARIYA et al., 1995). Muitos casos de efeitos colaterais geralmente associados ao uso de neurolépticos (parkinsonismo, acatisia, discinesia tardia) foram relatados, especialmente para o uso de flunarizina em pacientes idosos (CHOUZA et al., 1986).

Estudos subseqüentes demonstraram que a flunarizina é um antagonista de receptores D2 de dopamina (como todos os antipsicóticos), com afinidade moderada, além de apresentar baixo efeito anticolinérgico (BRÜCKE et al., 1995; HARAGUCHI et al., 1997). A afinidade da flunarizina para os receptores D2 é intermediária entre a da olanzapina e clozapina, que é a principal característica dos antipsicóticos atípicos, de acordo com Seeman (1997).

Os fatores de risco para desenvolver sintomas extrapiramidais com a flunarizina são idade (especialmente >70 anos), sexo feminino e uso prolongado (mais de seis meses). Este perfil é provavelmente devido à redução do tônus dopaminérgico com a idade e ao acúmulo da droga administrada diariamente e por longo prazo, apesar da meia-vida longa (KARIYA et al., 1995).

Apesar do perfil favorável para sua aplicação na psiquiatria, a flunarizina nunca foi considerada para o tratamento da esquizofrenia ou de transtornos psicóticos. Estudos prévios foram conduzidos para explicar a ocorrência dos sintomas extrapiramidais, o que limitou seu uso para as indicações terapêuticas habituais, ao invés de expandir seu potencial terapêutico como antipsicótico ou antimaníaco.

Existem somente dois relatos sobre o uso de flunarizina em psiquiatria. Em uma paciente com transtorno bipolar com 20 episódios maníacos prévios não responsivos ao tratamento com lítio, a flunarizina produziu um efeito terapêutico que foi atribuído às suas propriedades bloqueadoras dos canais de cálcio (LINDELIUS e NILSSON, 1992). Já Eckman (1985) relatou melhora significativa em pacientes com diagnóstico de depressão involutiva (segundo CID 9) associada a distúrbios cerebrovasculares após tratamento com flunarizina, comparado ao tratamento placebo.

Outro fator surpreendente é que a longa meia-vida de eliminação da flunarizina (2 a 7 semanas) (PLEDGER et al., 1994) é frequentemente desconsiderada na prática clínica, sendo normalmente prescrita na dose diária de 10 mg, sem redução de dose ou aumento do intervalo entre as doses após uso em longo prazo (mais de seis meses), quando os efeitos adversos podem ocorrer simplesmente devido ao acúmulo da droga. Poucos estudos adequadamente consideraram esta característica farmacocinética. Belfiore et al. (1998) observaram que o benefício para os movimentos coreicos depois de uma dose única de 20 mg de flunarizina em pacientes com Coréia de Huntington durava pelo menos uma semana. Pledger et al. (1994) conduziram um grande ensaio clínico com controle da concentração sérica da droga para tratamento da epilepsia refratária com crises parciais, sendo que uma estratégia de dose de carga ou de ataque foi usada e a redução da dose da flunarizina era permitida de acordo com os níveis séricos.

Além das características antidopaminérgicas, outros mecanismos pelos quais a flunarizina pode favorecer o tratamento da esquizofrenia e do transtorno esquizoafetivo são:

1. ***Bloqueio de canais de cálcio dos tipos T, L e N*** – o aumento na concentração intracelular de cálcio promove eventos como liberação de neurotransmissores, aumento da atividade sináptica, modulação de diversas enzimas e indução de morte celular. A flunarizina é um bloqueador não específico destes canais de cálcio com afinidade de moderada a alta, com relevância comportamental (HOLMES et al., 1984; AKAIKE et al., 1989; TYTGAT et al., 1991).
2. ***Bloqueio de canais de Na^+*** – este mecanismo é crítico na ação de muitos anticonvulsivantes (fenitoína, carbamazepina e lamotrigina) e reduz a despolarização neuronal e a liberação de neurotransmissores (CATTERALL, 1999). A flunarizina é um potente inibidor de canais de Na^+ baseado em estudos de *binding* de [^{3}H]-BTX-B a canais de Na^+ e em parâmetros eletrofisiológicos (VELLY et al., 1987; PAUWELS et al., 1991, GASIOR et al., 1995). Também foi demonstrado que este mecanismo preveniu a neurotoxicidade por antagonistas de receptores NMDA (FARBER et al., 2002), que constitui o modelo farmacológico para a disfunção glutamatérgica na esquizofrenia.
3. ***Aumento das ações mediadas pela adenosina*** – a adenosina é um importante neuromodulador que inibe a liberação da maioria dos neurotransmissores e foi proposto que o seu déficit pode estar envolvido na patofisiologia da esquizofrenia (LARA et al., 2006). É importante mencionar que agonistas de adenosina apresentam um perfil pré-clínico de antipsicótico atípico (LARA et al., 2006) e alopurinol e dipiridamol se mostraram efeitos benéficos como tratamento adjuvante da esquizofrenia (AKHONDZADEH et al., 2000; BRUNSTEIN et al., 2005). Além disso, antagonistas de receptores de adenosina como cafeína e teofilina podem exacerbar sintomas de

esquizofrenia (LUCAS et al., 1990), mimetizar o déficit de supressão do potencial evocado P50 (ADLER et al., 1998) e as alterações do sono (KESHAVAN et al., 1998) encontrados na esquizofrenia em voluntários normais (LANDOLT et al., 1995; GHISOLFI et al., 2002). Em um modelo animal, o efeito anticonvulsivante da flunarizina foi atenuado pelo pré-tratamento com a cafeína (POPOLI et al., 1990), possivelmente relacionada à capacidade da flunarizina em inibir a recaptação de adenosina (PHILLIS et al., 1983).

4. ***Efeito neuroprotetor*** - a flunarizina apresentou efeitos neuroprotetores em modelos de isquemia cerebral, lesões nervosas, privação de NGF e implante neuronal (POIGNET et al., 1989; TONG et al., 1997; BERGER et al., 1998; DISPERSYN et al., 1999; PATRO et al., 1999; KAMINSKI et al., 1999), o que pode favorecer a plasticidade neural por atenuar o postulado déficit de atividade trófica e atenuar a vulnerabilidade à excitotoxicidade e neurodegeneração na esquizofrenia.
5. ***Ação anticonvulsivante em animais e humanos*** – a esquizofrenia é associada a um risco aumentado de convulsões (HYDE e WEINBERGER, 1997) e alguns pacientes, especialmente esquizoafetivos, podem se beneficiar com o tratamento com anticonvulsivantes/estabilizadores do humor. Um ensaio clínico bem desenhado, controlado com placebo, com tratamento adjunto com flunarizina em doses ajustadas, focando o tratamento de crises parciais complexas mostrou uma significativa redução na freqüência de convulsões (PLEDGER et al., 1994). A flunarizina também é anticonvulsivante em modelos animais (POPOLI et al., 1990).
6. ***Efeitos cognitivos*** – a melhora do desempenho cognitivo após tratamento com flunarizina foi observada em idosos com síndrome cerebral orgânica (HEINZE et al., 1986) e em pacientes com doença cerebrovascular crônica (AGNOLI et al., 1988), o que pode ser

relevante para a esquizofrenia, já que a cognição é fundamental na síndrome e responsável por grande parte da morbidade e prejuízo funcional causada pela doença (REICHENBERG e HARVEY, 2007; BILDER et al., 2002).

A flunarizina não apresenta antagonismo significativo de receptores 5-HT e é um fraco antagonista de receptores H1 de histamina (HOLMES et al., 1984). Ela é geralmente bem tolerada e segura, como verificado também pelo seu uso freqüente e prolongado em idosos (com exceção do parkinsonismo quando a dose não é ajustada), sendo sonolência leve e ganho de peso de 2-4 Kg no longo prazo os efeitos adversos mais comuns. No ensaio clínico para epilepsia refratária, em que a flunarizina foi usada geralmente na dose diária de 30-40 mg, o ganho de peso médio foi de 3,9 kg após 25 semanas (PLEDGER et al., 1994).

I.5. Modelos animais

Em estudos pré-clínicos, a flunarizina foi eficaz em modelos farmacológicos com validade preditiva para antipsicóticos. A flunarizina produziu um efeito inibitório significativo contra comportamentos induzidos pelo agonista indireto de dopamina anfetamina em roedores e macacos (GREBB, 1986; ROSENZWEIG e BARRETT, 1995; HORI et al., 1998) e um efeito limítrofe sobre a locomoção induzida pelo PCP, um antagonista de receptores NMDA, que é o principal modelo farmacológico para a esquizofrenia (HORI et al., 1998). A flunarizina também preveniu, enquanto o haloperidol potencializou, os efeitos sobre o EEG induzidos pelo PCP (POPOLI et al., 1992; FEINBERG e CAMPBELL, 1998).

Tort et al (2005) avaliaram o efeito do tratamento prévio com flunarizina sobre a hiperlocomoção induzida por anfetamina (agonista dopaminérgico) e MK-801 ou dizolcipina (antagonista de receptores NMDA) em camundongos. A flunarizina (administrada 3 horas antes

por via oral) dose-dependentemente e significativamente inibiu a hiperlocomoção induzida por anfetamina e MK-801 em doses que não causaram catalepsia (Figuras 1 e 2), similarmente ao que já foi relatado para a olanzapina e a clozapina (NINAN e KULKARNI, 1999; O'NEILL e SHAW, 1999) e diferentemente do haloperidol, que inibe a locomoção induzida por MK-801 somente em doses que inibem a locomoção espontânea (O'NEIL e SHAW,1999).

Com base nessa série de dados, realizamos o ensaio clínico randomizado em que comparamos a flunarizina e o haloperidol no tratamento da esquizofrenia.

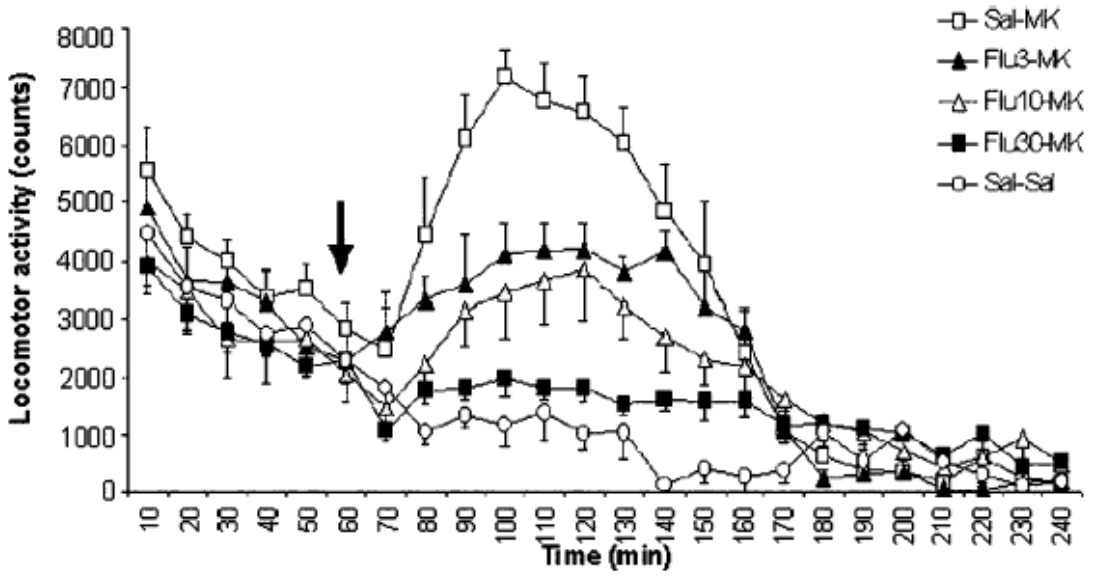

Figura 1 – A flunarizina dose-dependentemente inibiu a hiperlocomoção induzida por MK-801 em camundongos. A flunarizina foi oralmente administrada (3, 10 e 30 mg/kg) a camundongos machos albinos 3 horas antes de iniciar o registro da locomoção espontânea em um sistema computadorizado. Depois de uma hora de habituação, os camundongos foram injetados com 0.25 mg/kg de MK-801 i.p. e a locomoção foi registrada por mais 3 horas (n=6 por grupo). Resultados mostrados como média ± erro padrão. Estatística (ANOVA de duas vias com tempo como a medida repetida): sem diferença entre os grupos no intervalo 0-60 min e salina>flu3=flu10>flu30 ($p<0.05$) no intervalo 70-160 min.

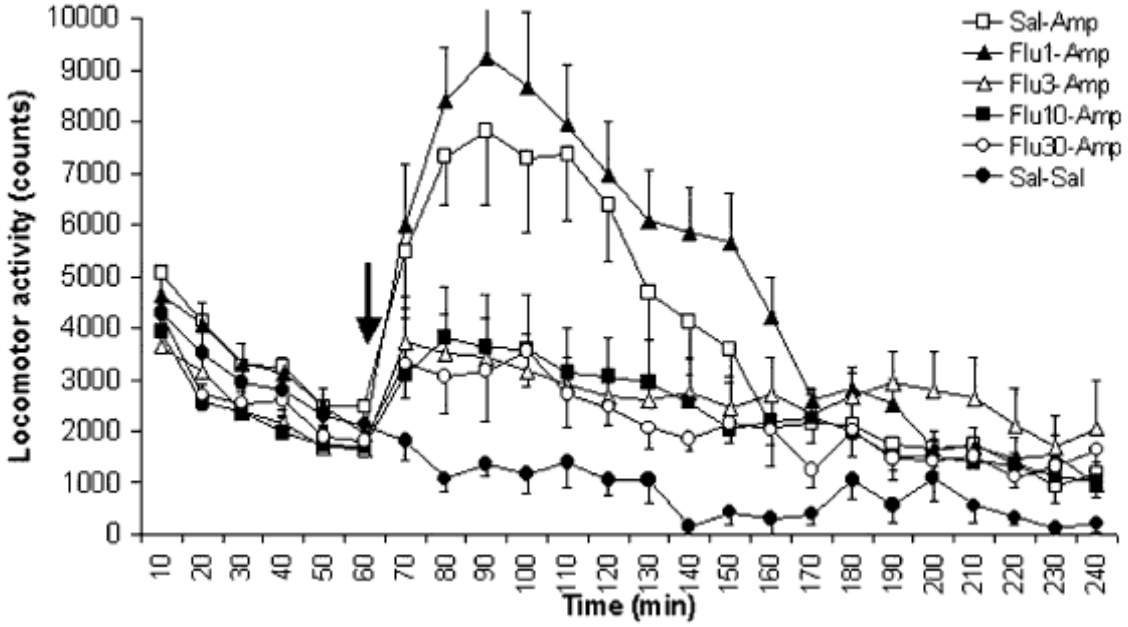

Figura 2 – A flunarizina dose-dependentemente inibiu a hiperlocomoção induzida por anfetamina em camundongos. A flunarizina foi oralmente administrada (3, 10 e 30 mg/kg) a camundongos machos albinos 3 horas antes de iniciar o registro da locomoção espontânea em um sistema computadorizado. Depois de uma hora de habituação, os camundongos foram injetados com 5 mg/kg de anfetamina ou salina i.p. e a locomoção foi registrada por mais 3 horas (n=6 por grupo). Resultados mostrados como média ± erro padrão. Estatística (ANOVA de duas vias com tempo como a medida repetida): sem diferença entre os grupos no intervalo 0-60 min e salina=flu1>flu3=flu10=flu30 ($p<0.05$) no intervalo 70-160 min.

PARTE II – LIMITAÇÕES DAS CLASSIFICAÇÕES VIGENTES

O DSM-IV TR e o CID-10 são as classificações atuais utilizadas no diagnóstico dos transtornos mentais e que têm o mérito de ter unificado terminologias em todo o mundo. Assim, um paciente com diagnóstico de Transtorno Depressivo Maior no Brasil provavelmente terá esse mesmo diagnóstico em outro país.

Entretanto, esses manuais conceituam os diagnósticos através da presença ou ausência de "critérios diagnósticos", utilizando pontos de corte oriundos de consenso de "experts" e fazendo uma avaliação centrada no momento presente, deixando de lado aspectos clínicos importantes como sintomas prévios, temperamento de base, presença de outros transtornos concomitantes, história familiar e resposta a fármacos.

O diagnóstico baseado nesses manuais é baseado na presença ou ausência de um número mínimo de sintomas (critérios diagnósticos) que devem estar presentes por um determinado período de tempo. Esses critérios não foram determinados com base em evidências científicas e muitas vezes não são satisfeitos em pacientes da realidade clínica.

Situações de comorbidades e quadros clínicos sublimiares ou subsindrômicos são apresentações freqüentes no âmbito clínico. No entanto são negligenciados e excluídos das pesquisas apesar da sua importância e complexidade.

Akiskal, Angst e outros autores têm proposto maior flexibilidade dos critérios diagnósticos e o conceito de espectro bipolar, além de características e especificadores que poderiam auxiliar no diagnóstico mais preciso e "ao longo da vida" (AKISKAL e PINTO, 1999; ANGST et al., 2003).

Lara et al. (2006) propuseram um modelo bidimensional com base no temperamento emocional e afetivo. Esse modelo é baseado em traços de inibição (medo e cautela) e de ativação (raiva e vontade), regulados por uma esfera chamada controle. Essa proposta contempla humor, comportamento e personalidade tanto normais quanto patológicos e sugere que os diagnósticos devam ser baseados na "natureza emocional" do paciente.

Do ponto de vista neuroquímico, a ativação é modulada por dopamina, glutamato e talvez noradrenalina, correspondendo em neuroanatomia ao estriado ventral e núcleo accumbens. A inibição é relacionada aos neurotransmissores serotonina e GABA, além da noradrenalina e vasopressina, tendo como regiões modulatórias a amígdala, área cinzenta periaquedutal e cíngulo anterior. O controle pode ser dividido em intrínseco (dentro das dimensões de ativação e inibição) e extrínseco (relacionado ao córtex frontal).

De acordo com esse modelo, traços de temperamento são fatores protetores ou de risco para o desenvolvimento de transtornos mentais e a moderação dos traços temperamentais é menos provavelmente associada com transtornos psiquiátricos. Como analogia, podemos pensar que o sistema humoral funciona como um tanque de água onde há uma entrada ou torneira (ativação), uma saída ou ralo (inibição), uma bóia (controle) e o nível do líquido (humor) (Figura 1).

Segundo essa proposta, os transtornos psiquiátricos estão relacionados ao excesso ou deficiência de ativação, inibição e/ou controle. Altos escores de ativação são centrais nos transtornos do espectro bipolar e excessos comportamentais (jogo, drogas, bulimia...), enquanto que a depressão é a redução da ativação (vontade). Os estados mistos compreenderiam a coexistência de altos escores de ativação e inibição, sendo a ativação expressa mais como raiva do que como vontade. Os transtornos de ansiedade caracterizam-se pelo excesso de inibição, a deficiência de controle é concebida como central no Transtorno de Déficit de Atenção e

Hiperatividade e o excesso de controle é um componente fundamental no Transtorno Obsessivo-Compulsivo.

Humor, afeto, comportamento, cognição, percepção, atenção, intenções e relações tendem a mudar no mesmo sentido e possuem substratos neuroquímico e neuroanatômico que se sobrepõem. O temperamento constituiria a força de ligação que influencia e é influenciada pelos fatores mencionados acima.

Com relação ao tratamento farmacológico, é proposto que o objetivo deve ser corrigir as desregulações temperamentais. Assim, os antipsicóticos de primeira geração são desativadores e os antipsicóticos de segunda geração são desativadores e desinibidores simultaneamente. Os inibidores seletivos da recaptação de serotonina são primariamente desinibidores, mas também levariam a um aumento da ativação, enquanto os antidepressivos com ação noradrenérgica e dopaminérgica são mais ativadores (regiões límbicas) e podem aumentar o controle (regiões frontais). Os benzodiazepínicos são desinibidores, o divalproato pode aumentar o controle e reduzir ativação e inibição, a oxcarbazepina e a carbamazepina podem regular o controle e também ser desativadores e o lítio principalmente aumentaria a inibição.

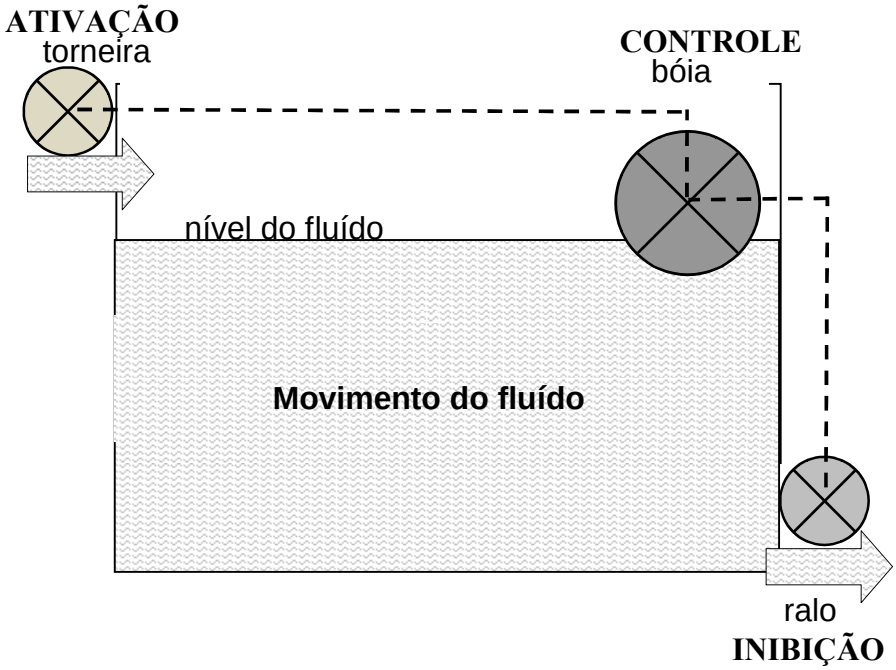

Figura 1 – Modelo do tanque de água, ilustrando os eixos de ativação, inibição e controle. O nível e a dinâmica do fluído corresponde aos temperamentos afetivos de Kraepelin/Akiskal. Ativação, inibição e controle são relacionados ao temperamento emocional, como na abordagem de Cloninger et al. Reproduzido com autorização de Lara et al (dados não publicados).

OBJETIVOS

Os trabalhos da presente tese foram divididos em dois capítulos: (1) o ensaio clínico com flunarizina e (2) relatos de caso sobre possíveis alternativas de tratamento medicamentoso em outras condições psiquiátricas.

Capítulo 1

Objetivo Geral – Investigar a flunarizina como potencial novo antipsicótico, com perfil atípico, longa meia-vida e de baixo custo.

Objetivos Específicos:

1.Revisar a literatura que dá suporte à hipótese que a flunarizina tenha propriedades antipsicóticas.

2.Avaliar o tratamento com flunarizina em pacientes esquizofrênicos em um ensaio clínico randomizado, duplo-cego, comparado com haloperidol.

Capítulo 2

Objetivo Geral – Descrever casos com apresentações diferenciadas e apresentar opções farmacológicas com base no temperamento.

Objetivos Específicos:

1.Conceituar alguns quadros clínicos a partir de um referencial teórico com base no temperamento emocional e afetivo.

2.Discutir hipóteses e possíveis mecanismos de ação das medicações nas situações apresentadas.

PARTE III – FLUNARIZINA COMO ANTIPSICÓTICO

Capítulo 1 – OS RESULTADOS DO ENSAIO CLÍNICO DE FLUNARIZINA VERSUS HALOPERIDOL

Is flunarizine a long-acting oral atypical antipsychotic? A randomized clinical trial versus haloperidol for the treatment of schizophrenia[1]

Running title: flunarizine as an atypical antipsychotic

Luísa W. Bisol[1], Miriam G. Brunstein[2], Gustavo L. Ottoni[1], Fernanda L. P. Ramos[2], Daniela L. Borba[3], Claudiane S. Daltio[4], Ricardo V. de Oliveira[1], Gisele E.G. Paz[3], Sayuri E. de Souza[4], Rodrigo A. Bressan[4], Diogo R. Lara[3]

1. Departamento de Bioquímica – ICBS – UFRGS, Porto Alegre, Brazil
2. Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
3. Faculdade de Biociências e Hospital São Lucas, PUCRS, Porto Alegre, Brazil
4. Proesq – Programa de Esquizofrenia and LiNC – Lab Interdisciplinar de Neurociências Clínicas, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil.

Corresponding author:
Diogo R. Lara
Faculdade de Biociências – PUCRS
Av. Ipiranga, 6681 Pd 12A
Porto Alegre – RS
Brazil
90619-900
E-mail: drlara@pucrs.br
Fax 55 51 33203612

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ABSTRACT

Flunarizine is known as a non-specific calcium channel blocker that has been used for decades for the treatment of migraine, vertigo and cognitive deficits related to cerebrovascular disorders. Flunarizine also has dopamine D2-receptor blocking properties and was effective in animal models of predictive validity for antipsychotics. However, its clinical antipsychotic efficacy has never been investigated.

Objective: To evaluate the therapeutic efficacy and tolerability of flunarizine compared to haloperidol in outpatients with stable and chronic schizophrenia and schizoaffective disorder.

Method: Seventy patients from two centers were randomized and participated in a double-blind, parallel-group, flexible-dose study comparing flunarizine (10-50 mg/day) and haloperidol (2.5-12.5 mg/day) for 12 weeks. Patients were assessed with the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (CGI) Improvement scale, Extrapyramidal Symptom Rating Scale (ESRS), a battery for cognitive performance and laboratory exams.

Results: Mean dose at endpoint were 29.7 mg/day for flunarizine and 6.4 mg/day for haloperidol. Both groups showed significant symptom improvement during the study, with a reduction of 21% in the flunarizine group and 19% in the haloperidol group in PANSS total scores. There were no significant differences in PANSS overall score and all subscales, CGI or cognitive performance. Drop-out rates, ESRS scores and prolactin levels were not different between groups, but significantly more patients reported emergence of akathisia in the haloperidol group, and weight gain was significantly higher with flunarizine (1.2 kg) than with haloperidol (-0.8 kg) ($p<0.05$).

Conclusion: This is the first study evaluating flunarizine's antipsychotic properties, which showed good efficacy and tolerability for the treatment of schizophrenia, with a possible atypical profile. Its unique pharmacokinetic profile as an oral drug with long half life (2-7 weeks), low cost and low induction of extrapyramidal symptoms, warrants further investigation, particularly in psychiatric patients with low adherence to treatment.

Key-words: Schizophrenia. Antipsychotic. Flunarizine. Clinical trial

INTRODUCTION

Large amounts of research have demonstrated that D2 dopamine receptor blockade is associated with antipsychotic activity[1,2]. More recently, moderate D2 receptor blockade has been suggested as a common feature among atypical antipsychotics[3], which were an important advance in the treatment of schizophrenia and other psychotic disorders[4]. However, there are concerns about metabolic and cardiovascular side effects[4] and another major issue is their high cost, making them inaccessible for many patients, especially in low and middle income countries.

The diphenylpiperazine flunarizine has been used in some countries for the treatment of migraine[5], vertigo[6] and cognitive deficits related to cerebrovascular disorders[7,8]. These effects been attributed to its non-specific blockade of calcium channels, along with sodium channel blockade that may contribute to its anticonvulsant properties[6]. However, many cases of neuroleptic-like side-effects (parkinsonism, akathisia, tardive diskynesia) have been reported[9], discouraging its prolonged use particularly in the elderly[10]. As expected, subsequent studies found that flunarizine is a dopamine D2 receptor antagonist of moderate affinity, with low anticholinergic activity[11,12]. Specifically, the affinity of flunarizine for D2 receptors is in the range between olanzapine and clozapine, which is one of the main characteristics of atypical antipsychotics[3]. In a SPECT study, the D2 blockade produced by flunarizine 10 mg daily for at least 1 month was around 40-50%[10], whereas antipsychotic activity without major extrapyramidal side-effects is usually seen with D2R blockade between 65 and 80%[13]. Flunarizine lacks significant 5-HT receptor blockade and is a mild histamine H1 receptor blocker[14].

In pre-clinical studies, flunarizine was effective in pharmacological models with predictive validity for antipsychotics. Flunarizine produced significant inhibitory effects against behavior alterations induced by the dopamine agonist amphetamine in rodents and monkeys[15,16,17] and the NMDA receptor antagonists PCP and MK-801 in rodents[17,18]. This profile involving both dopamine and glutamate models is similar to atypical antipsychotics, whereas typical antipsychotics fail to attenuate the effects of NMDA receptor antagonists[19]. Of note, flunarizine also prevented[20], whereas haloperidol potentiated (by mechanisms other than D2 receptor antagonism), the EEG effects of PCP[21].

Despite this clinical and preclinical profile, flunarizine has not been considered for the treatment of schizophrenia or psychotic disorders. All studies were conducted to explain the emergence of extrapyramidal side-effects, which limited its use for its regular indications, rather

than taking into consideration its potential therapeutic effect as an antipsychotic. Furthermore, flunarizine has been fully tested for migraine and vertigo and is generally well-tolerated and safe. It has a unique pharmacokinetic for an oral drug, a long half-life of 2-7 weeks[22], which may be an important advantage for psychotic patients with low adherence to treatment. Thus, the aim of the present study was to evaluate the efficacy of flunarizine compared to haloperidol in the treatment of schizophrenia and to evaluate parameters that are proposed to favor atypical in comparison to typical antipsychotics, such as psychiatric and extrapyramidal symptoms[23], and cognitive performance[24].

MATERIALS AND METHODS

Patients

Male or female outpatients with schizophrenia or schizoaffective disorder (DSM-IV) between 18 and 65 years old with a PANSS score above 45 were included in the study. They were recruited from 2 sites in Brazil (Porto Alegre and São Paulo). Exclusion criteria included unstable clinical disease, pregnancy, drug dependence (except for nicotine) in the past month, history of being refractory to at least 2 antipsychotics taken appropriately or use of clozapine. Both the patient and the authorized legal representative signed a written informed consent form after one of the researchers explained the study in detail. The study protocol was approved by local ethical review boards and the National Council of Research Ethics, and carried out in accordance with the Declaration of Helsinki.

Study Design

This was two-center randomized, double-blind, parallel-group, flexible-dose study comparing flunarizine and haloperidol for 12 weeks. Screening phase consisted of screening tests, medical history, psychiatric examination and scheduling of washout if necessary (1-3 weeks for down-titration all other medications and 3 to 7 days washout period of other antipsychotics). Treatment phase was the 12-week double-blind therapy period, with haloperidol and flunarizine deliver in identical pills. Patients were randomly assigned at a 1:1 ratio to haloperidol 5 mg daily (2 pills with 2.5 mg at night) for 3 weeks or flunarizine loading dose of 40 mg a day (2 pills of 20 mg at night) for 7 days (total 280 mg), followed by a daily dose of 20 mg (2 pills with 10 mg at night). Haloperidol dose could be altered up or down by 2.5 mg every 3

weeks, with minimum and maximum daily doses of 2.5 and 12.5 mg. Flunarizine dose could be altered up or down by 10 mg every 3 weeks, with minimum and maximum daily doses of 10 and 50 mg. This loading dose scheme (40 mg/day for 7 days) was created based on a NIH-funded study of flunarizine for refractory epilepsy[22], where the loading dose was calculated after pharmacokinetic characterization of a single-dose flunarizine for each patient, which was unfeasible for us. In that study, the minimum loading dose was 257 mg. Over 90% of the patients were assigned doses above 20 mg/day and 75% were kept on doses between 20 and 50 mg/day. Importantly, even with such aggressive strategy, only 8 out of 46 patients discontinued the study. Therefore, our strategy seeks to reach therapeutic levels based on a safe and well-tolerated fixed loading scheme (280 mg in 7 days), a moderate initial maintenance dose (20 mg) and dose adjustment based on efficacy and tolerability.

Adjunctive treatments were allowed after 1 week of treatment with the study drugs. Biperiden up to 4 mg and promethazine 25 to 50 mg a day could be prescribed for extrapyramidal symptoms and insomnia, respectively.

Assessments

The primary efficacy measure was the score on the Positive and Negative Syndrome Scale (PANSS – items score from 1 to 7) at baseline and weeks 3, 6, 9 and 12. The CGI Improvement scale was used to evaluate overall improvement at weeks 1, 3, 6, 9 and 12, with the previous visit as reference. Cognitive performance was assessed at baseline and week 12 with the following tests: logical memory and visual reproduction from the Wechsler Memory Scale; Trail Making Test; the computerized version of Wisconsin Card Sorting Test; Digit Span, Block Design and Digit Symbol from WAIS-R; and Stroop Test.

Regarding safety and tolerability, extrapyramidal symptoms were assessed using Extrapyramidal Symptom Rating Scale (ESRS) at baseline and weeks 1, 3, 6, 9 and 12, and laboratory tests (including prolactin) and weight were evaluated at baseline and week 12.

Statistical Analysis

Demographic and baseline values were compared between flunarizine and haloperidol groups with T-test, except for gender, which was evaluated with Fisher's exact test, and extrapyramidal symptoms, which were evaluated with Mann-Whitney test.

The primary outcome of the study was change in PANSS subscales and total scores, which were evaluated using the last-observation-carried-forward (LOCF) method. Analysis was performed using two approaches: 1) change from baseline to last week of treatment using T-test and 2) repeated-measures analysis of variance with scores at baseline and weeks 3, 6, 9 and 12 as dependent variables, with time as a within-subject repeated measure, and treatment group (haloperidol and flunarizine) as a between-subjects fixed factor. These analyses were also performed for completers of the 12 weeks of the study. Other secondary outcomes were extrapyramidal symptoms, including akathisia, performance in the cognitive battery, use of biperiden and promethazine, prolactin levels, weight and percentage of dose change in the flexible dose regimen between groups, which were analyzed as change from baseline to last week of treatment using T-test. To correct for multiple comparisons, Bonferroni procedure with Finner's modification was used. Incidence of adverse events was compared with Fisher's exact test. All statistical tests were two-sided with significance level at 5%. All analyses were performed with SPSS 11.0.

RESULTS

Patients and Treatment

The patient flow chart is shown in Figure 1. From 232 patients evaluated, 70 patients met the inclusion criteria and were willing to participate in the study. Fifty-two of the 70 patients who were enrolled completed the 12 weeks of evaluation. Sixty patients were enrolled at the Porto Alegre site and 10 at the São Paulo site. Patients' demographics and illness characteristics are shown in Table 1. No statistical differences were observed between the baseline values of patients in the flunarizine and haloperidol groups, including extrapyramidal symptoms (0.08 for parkinsonism and 0.06 for akathisia, Mann-Whitney test). Completion rates and discontinuation due lack of efficacy were not different between both treatment groups. No serious adverse events were reported, except for 1 case of acute dystonia in a patient on haloperidol during the first week of treatment, which lead to interruption of treatment. One patient in the flunarizine group and 1 patient in the haloperidol group were hospitalized for exacerbation of schizophrenia.

There was also a non-significant trend ($p=0.07$) towards more dose increments during the study in the flunarizine group, which ended the study with a mean dose of 29.7 ± 10.0 mg/day (49% increase over the 20 mg/day baseline dose after 1 week of loading dose) compared

to 6.4 ± 2.0 mg in the haloperidol group, which was a 28% increase over the 5 mg/day baseline dose.

Efficacy

Both flunarizine and haloperidol were associated with significant improvements from baseline to week 3 onwards in all PANSS subscales and total scores ($p<0.05$), as shown in Figure 2. There was a reduction of 21% in the flunarizine group and 19% in the haloperidol group in PANSS total scores. However, there was no statistical difference between both groups in any of the PANSS subscales or total score ($p>0.10$). The same was true for the analysis of completers only, despite a numerically superior improvement with haloperidol on positive symptoms and with flunarizine in negative and general symptoms (Figure 2, left column). Mean CGI Improvement scores during the study were not different between groups (flunarizine=3.7 ± 0.9 and haloperidol= 3.8 ± 1.0, LOCF).

Regarding cognitive performance, the group as a whole showed statistically significant improvement in 13 of the 22 parameters evaluated. However, there were no significant differences between groups in change of test scores.

Safety and Tolerability

There were no differences between groups in change of extrapyramidal symptoms and akathisia scores measured with ESRS or use of promethazine or biperiden (Figure 3). However, more patients experienced treatment-emergent akathisia (i.e. an increase compared to baseline score) in the haloperidol group (16 out of 36 patients) than in the flunarizine group (7 out of 34 patients, $p=0.04$, Fisher's exact test). Although parkinsonism and akathisia scores at the end of study were higher in the haloperidol group, their baseline levels were also higher than in the flunarizine group. There was a numerically but non-significantly higher use of promethazine and biperiden in the haloperidol group (Figure 3).

In terms of prolactin concentrations, there were no differences between groups at entry or end of the study (flunarizine baseline = 13.0 ± 20.6 ng/ml and after treatment = 20.8 ± 15.1 ng/ml haloperidol baseline = 10.2 ± 8.0 ng/ml and after treatment = 14.7 ± 8.2 ng/ml), but 12 out of the 25 completers in the flunarizine group and 10 out of the 27 completers in the haloperidol group had levels higher than the normal range at the end of the study. Galactorrhea or

amenorrhea were not reported by any patient during the study. Regarding weight changes among completers, patients on flunarizine showed a mean weight gain of 1.2 ± 2.9 kg (2 patients showed a higher than 7% weight gain) compared to a reduction of 0.85 ± 3.4 kg in the haloperidol group (2 patients showed a higher than 7% weight gain) ($p<0.05$, Student's t-test). Incidence of other adverse events showed no significant difference between groups (Table 2 - Fisher's exact test, $p>0.20$).

DISCUSSION

This is the first study testing the antipsychotic properties of flunarizine, a non-specific calcium channel blocker used for decades for the treatment of migraine, vertigo and cognitive deficits. This randomized double-blind haloperidol controlled trial suggests that flunarizine has good efficacy for the treatment of schizophrenia. Flunarizine was well tolerated, exerting minimal extrapyramidal effects and akathisia, usually not requiring biperiden or promethazine treatment. Overall, this profile is more characteristic of that of atypical or second-generation antipsychotics. However, prolactin levels were comparable to those of haloperidol and often surpassed the normal range, but no case of galactorrhea occurred. Although weight gain was modest during the study, it was significantly higher in the flunarizine group. There was a mean 1.2 kg increment during 12 weeks of flunarizine compared to a loss of weight in the haloperidol group, suggesting that the magnitude of weight gain is probably not a major drawback for this patient population. Flunarizine has been used to treat cognitive deficits in stroke patients and might contribute to minimize cognitive deficits in schizophrenia. In our study, both groups have presented improvements in the cognitive profile. Statistical power was low and the study duration relatively short to detect cognitive performance differences. Future studies on flunarizine's antipsychotic properties should further investigate these cognitive dimensions.

It should be noted that in this study haloperidol was used according to the best clinical practice, contrary to many studies that have used starting or target doses above 10 mg. High doses of haloperidol induce extrapyramidal symptoms in most patients[25,26], lead to early discontinuation and impair the blinding procedure. The adequacy of the dose regimen was confirmed with the findings that only a 28% mean rise in the haloperidol dose was necessary during the study, few patients showed symptom exacerbation and many patients did not require antiparkinsonian medication. However, this approach, along with higher baseline values in the

haloperidol group, probably contributed to the lack of statistical significance in most EPS measures compared to flunarizine.

To our knowledge, there are only two reports on use of flunarizine in psychiatry. In a patient with bipolar disorder with 20 previous manic episodes unresponsive to lithium, flunarizine produced a sustained therapeutic effect that was attributed to its calcium-channel blocking properties[27]. Eckmann[28] reported far better improvement with flunarizine compared to placebo for ICD involutional depression associated with cerebral circulatory disturbances. Conversely, many small studies and case reports suggest that flunarizine can induce depressive as well as extrapyramidal symptoms[29]. Risk factors for developing extrapyramidal symptoms with flunarizine treatment were age (especially >70 years old), female sex and long-term use (usually more than 6 months). This profile is probably due to the age-associated decay of dopaminergic tone and drug accumulation, since the half-life of flunarizine is 2-7 weeks[22,30].

The long half-life of flunarizine (2-7 weeks) may be an interesting feature in clinical practice. Flunarizine is possibly effective as an oral long-acting atypical antipsychotic, but this has to be tested. Its long half-life may also prevent early psychotic outbreaks due to interruption of treatment, which is often the case in this patient population. This feature may allow more time to reinstall treatment without significant clinical worsening. The long elimination half-life of flunarizine has been overlooked in clinical practice, being normally prescribed at 10 mg daily, without dose reduction after long term use (when side-effects can occur due to drug accumulation) or longer intervals between doses. Only two studies adequately considered this pharmacokinetic characteristic. Belfiore et al.[31] found that the benefit for choreic movements after a single 20 mg dose of flunarizine in patients with Huntington's chorea lasted at least 1 week, whereas Pledger et al.[22] conducted a large concentration-controlled trial for treatment of refractory partial seizures where a loading dose strategy was used and dose-reduction was allowed based on flunarizine serum levels. As expected with such long half-life, rats treated daily with flunarizine presented an almost linear accumulation of the drug in plasma and the striatum[30].

In general, the loading dose regimen of 40 mg/day for a week was very well tolerated. Along with the finding that the mean maintenance dose of flunarizine was increased from 20 to 30 mg during the study, we suggest that in clinical practice the most effective regimen may start with 50 to 60 mg/day for a few days, which can be tapered down to around 30 mg as a maintenance dose. This is similar to the regimen in the NIH study in epilepsy[22]. However, given

the long half-life of flunarizine (2-7 weeks), the daily dose may need to be reduced after long-term treatment. With this half-life and the fact that the loading dose was well tolerated also opens the possibility that flunarizine may be taken weekly.

Flunarizine has other actions that may provide additional benefit for the treatment of schizophrenia and schizoaffective disorders, such as neuroprotective and neurotrophic effects in models of cerebral ischemia[32,33], nerve lesions[34,35], NGF-deprivation and neuronal grafting[36,37], anticonvulsant activity in animals[20,38] and humans[22] and cognitive-enhancing effects[5,39]. In order to investigate if this profile translates into clinical benefits, other patient profiles, longer periods of treatment and larger samples are needed.

The major limitations of this study are the relatively small sample size, lack of a placebo arm and baseline severity of symptoms that is somewhat low for an optimal test of efficacy. Taking into account that 16% of patients in the haloperidol group abandoned the study due to lack of efficacy, compared to a 44% relapse rate 3 months after antipsychotic is withdrawn according to a meta-analysis[40] , our study had 73.6% power to detect differences at 0.05 level if flunarizine had no antipsychotic activity. Also, the dose regimen of flunarizine may have been slightly lower than optimum, since the dose had to be raised by 49% to a mean of ~30 mg/day. Somewhat higher ESRS baseline scores in the haloperidol group and use of adjuvant medications may also have impaired the analysis of motor side effects.

In summary, this clinical trial provides preliminary evidence that flunarizine is an orally effective, well-tolerated, and long-acting antipsychotic, with possible atypical properties. Its long acting effects could be specially useful for patients with low adherence to treatment. Flunarizine is commercially available in many countries, usually at low cost, therefore being a clinical option in many settings. Given its efficacy and good tolerability in this preliminary trial, along with its unique pharmacological profile, flunarizine should be further studied, particularly in schizophrenic and bipolar patients.

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Figure legends

Figure 1 – Patient flow chart.

Figure 2 – Effect of flunarizine and haloperidol on PANSS subscales and total score. Left column shows results of last observation carried forward (n=35 in flunarizine group and 36 in haloperidol group) and right column shows results among completers (n=25 in flunarizine group and 27 in haloperidol group). A and B for positive symptoms, C and D for negative symptoms, E and F for general symptoms, G and H for total PANSS score. No statistical difference was observed between groups in any measure ($p>0.1$).

Figure 3 – Adverse events, adjuvant medication and dose change during the study. A shows parkinsonian symptoms measured with ESRS, B shows akathisia score, C shows promethazine dose, D shows biperiden dose and E shows percentage of dose change compared to baseline flunarizine (20 mg/day) and haloperidol (5 mg/day) dose. All results are using last observation carried forward.

Table 1. Baseline demographic variables and illness characteristics.

	Flunarizine group (n=34)	Haloperidol group (n=36)
Age (y)	36.6 ± 9.1	34.1 ± 11.2
Gender (M/F)	25/10	28/8
Years of education	7.7 ± 2.8	9.3 ± 3.1
Age at diagnosis (y)	21.7 ± 4.6	21.9 ± 5.5
Number of hospital admissions	7.1 ± 10.6	3.6 ± 3.7
Typicals/atypicals/no antipsychotic/adjuvant	24/11/5/13	12/31/3/16
Chlorpromazine equivalents	360.8 ± 240.5	417.1 ± 297.6
PANSS scores		
Positive	14.6 ± 5.6	15.6 ± 5.1
Negative	21.1 ± 7.0	19.2 ± 7.5
General	32.6 ± 9.0	31.0 ± 7.7
Total score	68.4 ± 18.5	65.7 ± 15.2
Extrapyramidal Symptom scores		
Parkinsonism	0.44 ± 0.89	0.94 ± 1.32
Akathisia	0.06 ± 0.34	0.33 ± 0.86

Data shown as means ± SD. No significant difference were found between groups (t test and Mann-Whitney). Adjuvant = number of patients on adjuvant treatment with antidepressants, mood stabilizers or benzodiazepines. PANSS = Positive and Negative Syndrome Scale.

Table 2. Incidence of Treatment-Emergent Adverse Events

	Haloperidol group		**Flunarizine group**	
	N=36		**N=34**	
Adverse event	N	%	N	%
Insomnia	12	33.3	12	35.3
Parkinsonism	12	33.3	9	26.5
Akathisia	8	22.2	5	14.7
Agitation	8	22.2	5	14.7
Headache	4	11.1	1	2.9
Dystonia	4	11.1	1	2.9
Aggression	3	8.3	3	8.8
Anxiety	3	8.3	1	2.9
Somnolence	3	8.3	8	23.5
Body pain	2	5.5	3	8.8
Appetite increase	2	5.5	1	2.9
Dyskinesia	2	5.5	2	5.9
Appetite decrease	1	2.7	3	8.8
Dizziness	1	2.7	3	8.2

Figure 1

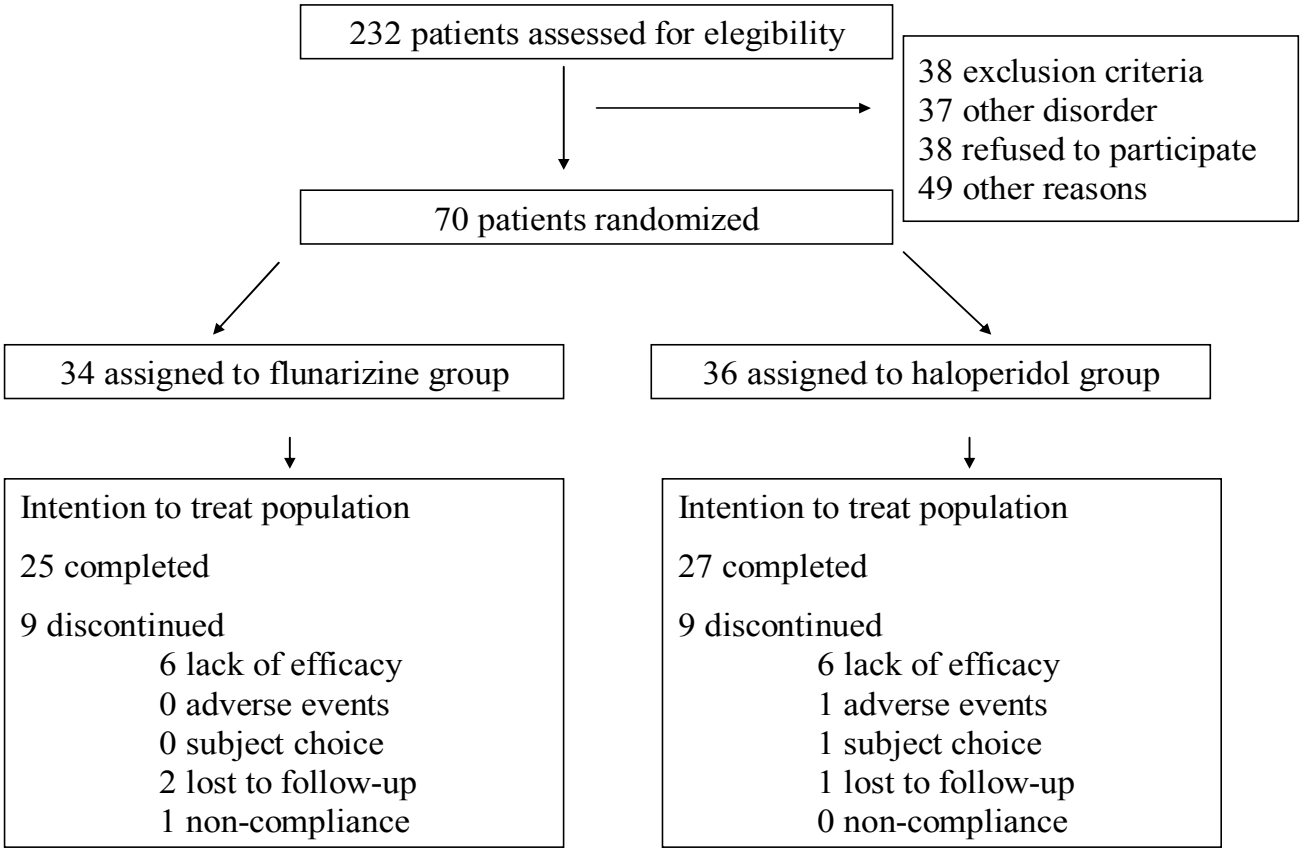
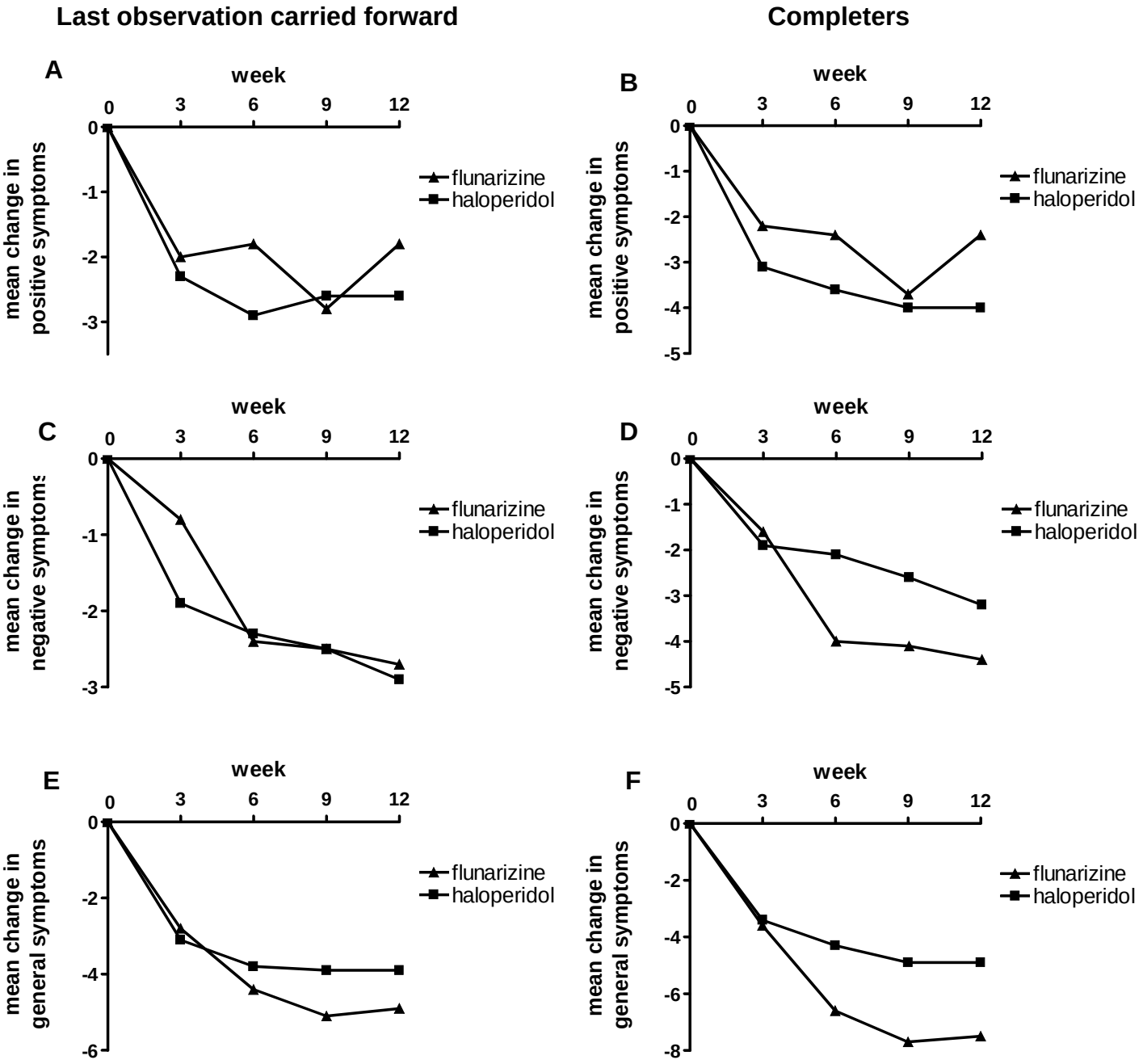

232 patients assessed for elegibility
38 exclusion criteria
37 other disorder
38 refused to participate
49 other reasons
70 patients randomized
34 assigned to flunarizine group
36 assigned to haloperidol group
Intention to treat population
25 completed
9 discontinued
6 lack of efficacy
0 adverse events
0 subject choice
2 lost to follow-up
1 non-compliance
Intention to treat population
27 completed
9 discontinued
6 lack of efficacy
1 adverse events
1 subject choice
1 lost to follow-up
0 non-compliance

FIGURE 2


Last observation carried forward
Completers
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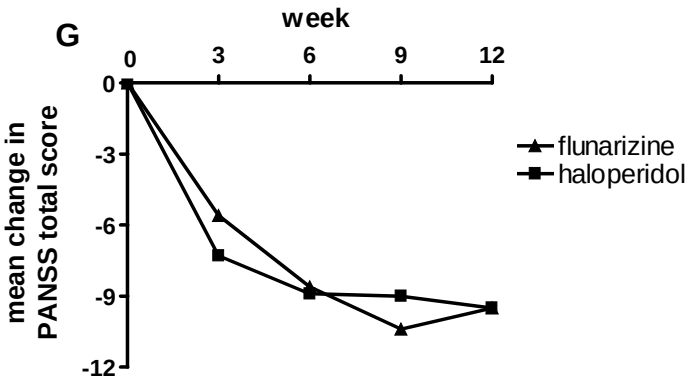
mean change in positive symptoms
mean change in negative symptoms
mean change in general symptoms
flunarizine
haloperidol


G
week
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6
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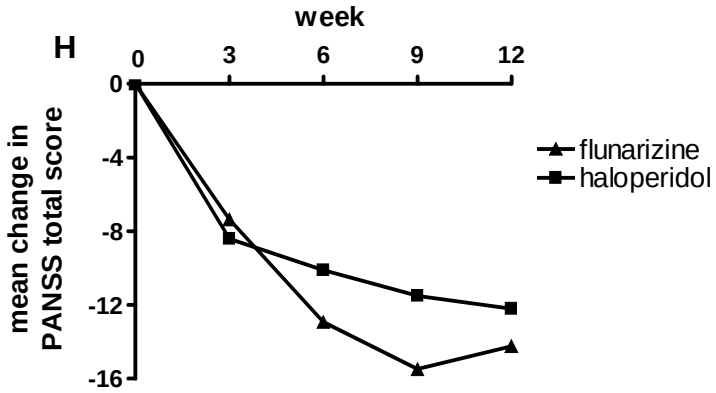
-3
-6
-9
-12
mean change in PANSS total score
flunarizine
haloperidol


H
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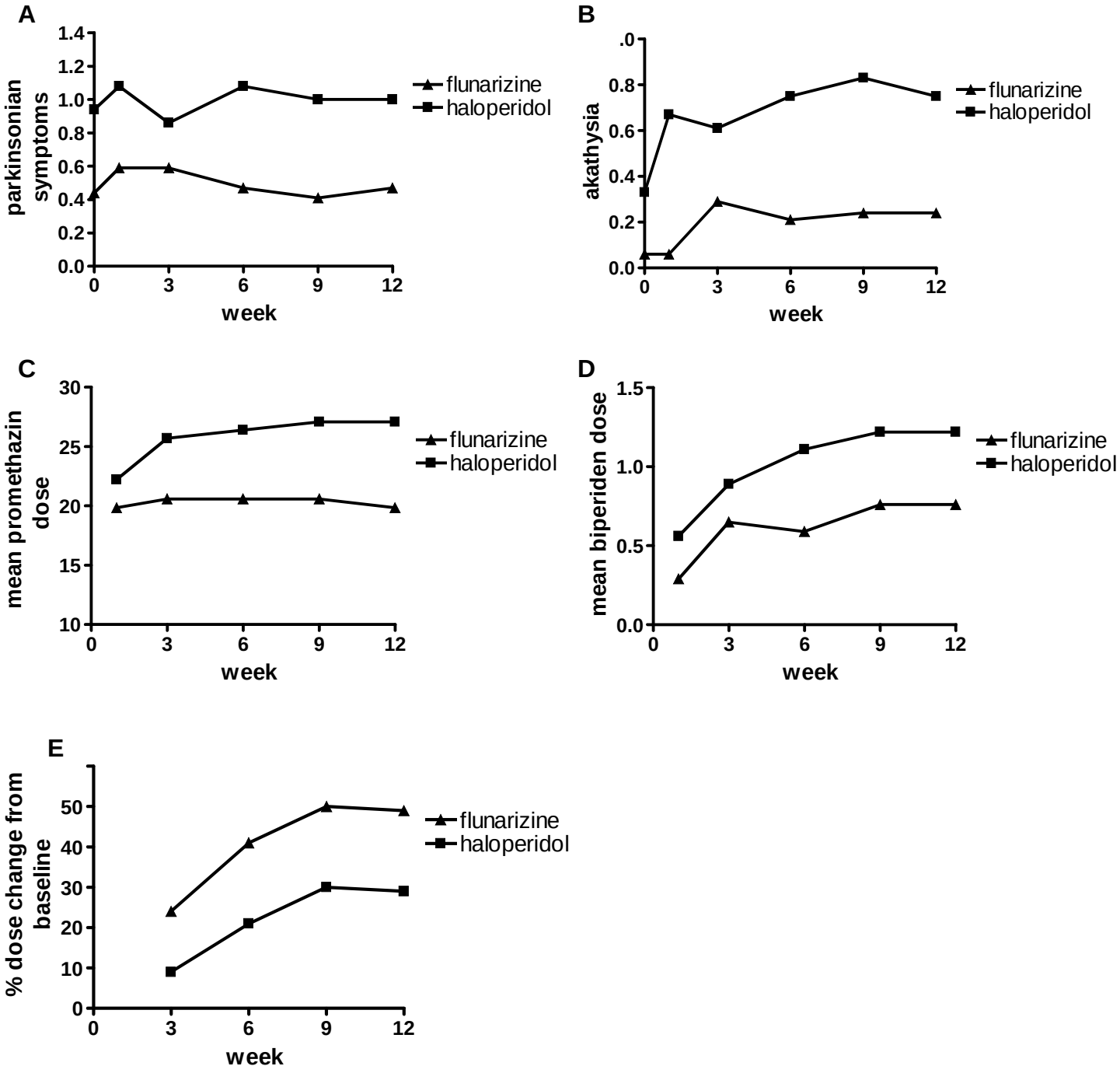
-4
-8
-12
-16
mean change in PANSS total score
flunarizine
haloperidol

FIGURE 3


A
parkinsonian symptoms
1.4
1.2
1.0
0.8
0.6
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0.0
0
3
6
9
12
week
flunarizine
haloperidol
B
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.0
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0.6
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3
6
9
12
week
flunarizine
haloperidol
C
mean promethazin dose
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25
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10
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9
12
week
flunarizine
haloperidol
D
mean biperiden dose
1.5
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3
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week
flunarizine
haloperidol
E
% dose change from baseline
50
40
30
20
10
0
0
3
6
9
12
week
flunarizine
haloperidol

Capítulo 2 – OS RELATOS DE CASO

1. Risperidona e ciúme patológico[2]

2. Lamotrigina e Divalproato no Transtorno Obssessivo-Compulsivo[3]

3. Quetiapina como regulador emocional[4]

[2] Status: aceito para publicação no Journal of Clinical Psychopharmacology
[3] Status: submetido para publicação na Pharmacopsychiatry
[4] Status: submetido para publicação no Journal of Psychopharmacology

LOW DOSE RISPERIDONE FOR PATHOLOGICAL JEALOUSY: REPORT OF THREE CASES

Luísa W. Bisol, MD, Departamento de Bioquímica, ICBS, UFRGS, Porto Alegre, Brazil

Diogo R. Lara, MD, PhD, Faculdade de Biociências, PUCRS, Porto Alegre, Brazil

Luísa W. Bisol

Departamento de Bioquímica - ICBS - UFRGS

Av. Iguaçu, 451/201

Porto Alegre - RS

Brazil

90470-430

e-mail: lwbisol@gmail.com

To the Editors:

Pathological jealousy is a persistent and poorly understood mental syndrome. This condition is characterized by extreme suspicion and causes suffering or impairs the functioning of the affected individual and the partner. The distinction between 'normal' and 'pathological' jealousy is difficult and is based on intensity of emotional response and lack of apparent reason for suspicion of a partner's fidelity. This condition modifies thoughts, feelings and behaviors of the patient and significant jealousy may affect up to 10% of individuals[1].

Currently the best level of evidence for the treatment of pathological jealousy comes from case reports on the efficacy of antidepressants (SSRIs) or typical antipsychotics (pimozide)[2,3.] These contrasting treatment options may reflect a clinical picture that shares anger (related to paranoia) and fear traits (related to anxiety, obsessive symptoms and insecurity)[4]. As we have suggested[5], the profile of atypical antipsychotics may be particularly useful for the treatment of both excessive anger (due to D2 receptor blockade) and fear (due to 5-HT2A, receptor blockade) symptoms or traits.

Risperidone is an atypical antipsychotic that blocks D2, 5-HT2A, α1 and H1 receptors[6]. Low dose risperidone (0.5-1.5 mg/day) has been used as an augmentation strategy for the treatment of refractory OCD[7], other anxiety disorders[8,9] and irritable and aggressive symptoms[10].

We describe three cases of patients with pathological jealousy without meeting the DSM-IV criteria for Paranoid Personality Disorder. They presented remission of jealousy symptoms with low doses of risperidone, without significant adverse events.

Case 1. A 30-year-old man with no DSM-IV psychiatric disorder used to check his partner's e-mail and follow her without her consent. He had recurrent and uncontrollable thoughts about the suspicion of his partner's infidelity. These symptoms were accompanied by intense guilt, suffering and awareness of

his exaggerated suspicions. He had undergone 2 years of psychotherapy, which he considered generally beneficial, but not for his jealousy. He was treated with risperidone up to 1mg/d with remission of symptoms after two weeks treatment. He has remained well without adverse reactions for 18 months.

Case 2. A 51-year-old white man had followed his wife at least once a week and had persistent suspicions about his wife's fidelity for about 4 months. He reported trivial events (e.g. his wife went in and out of a building, staying there for half an hour) as highly suggestive of betrayal. His wife threatened to divorce him if this behaviors persisted. He was otherwise functional and had no other psychiatric symptoms, but had a transient history of drug abuse and aggressive behavior during adolescence and mild paranoid traits that did not interfere with his life. Thus, he can be understood as having a delusional disorder of the jealous subtype. Within 2 weeks of risperidone 0.5 mg/day his symptoms remitted and he remained well for 14 months. The medication was tapered off, without reemergence of symptoms.

Case 3. A 41-year-old white woman with cyclothymic disorder had persistent thoughts about her husband's infidelity with no base on evidence. She was started on lamotrigine 25mg/d and oxcarbazepine 600mg/d. In her second consultation, the dose of lamotrigine was increased by 50mg/d, which were associated with worsening of jealousy symptoms. Lamotrigine was withdrawn and risperidone 1mg/d was started. She reported dramatic improvement of her paranoid symptoms about her husband and has remained well for 6 months.

These case reports suggest that low dose risperidone can be useful for the treatment of pathological jealousy. Schreiber et al.[11] had reported a similar improvement with risperidone in a patient who developed delusional jealousy after traumatic brain injury. Both serotonergic antidepressants and high potency antipsychotics (pimozide) have been advocated for the treatment of pathological jealousy[2,3]. Risperidone may be an option that combines both anti-delusional/anti-aggressive and anxiolytic properties associated with D2 and 5-HT2 receptors blockade[5]. Also, a link between obsessive compulsive disorder and pathological jealousy has been suggested[1] and risperidone has been useful for the treatment of this disorder[7].

These reports also support the notion that low dose risperidone (0.5-1.5 mg/day) can be helpful for milder cases, thus supporting the notion of a dimensional use of risperidone for mental disorders. Such low doses are usually well tolerated can be useful for patients without major psychotic disorders, especially those with disorders associated with high anger and high fear traits simultaneously.

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IMPROVEMENT OF OBSESSIVE-COMPULSIVE DISORDER WITH DIVALPROEX AND LAMOTRIGINE IN TWO PATIENTS WITH BIPOLAR II DISORDER

Luísa W. Bisol, MD, Departamento de Bioquímica, ICBS, UFRGS, Porto Alegre, Brazil

Diogo R. Lara, PhD, Faculdade de Biociências, PUCRS, Porto Alegre, Brazil.

Luísa W. Bisol

Departamento de Bioquímica - ICBS - UFRGS

Av. Iguaçu, 451/201

Porto Alegre - RS

Brazil

90470-430

e-mail: lwbisol@gmail.com

To the Editors:

Divalproex (DVP) and lamotrigine (LMT) have been used as mood stabilizers for the treatment and the prevention of recurrence of bipolar disorder. The first is recommended for treatment of acute mania and maintenance treatment of bipolar disorder (BD) and the latter is useful for prevention of bipolar depressive episodes.

The lifetime prevalence of the bipolar spectrum disorders is 4.4-6.5% of the general population[1,2]. Comorbidity of obsessive compulsive disorder (OCD) was found in 10-25% of bipolar I and II patients[2,3], with a negative impact on course and treatment of BD[4].

The treatment of patients with both conditions (BD and OCD) is a therapeutic dilemma because effective treatments of OCD, such as high-dose serotonin reuptake inhibitors (SRIs), could cause switching to mania and rapid cycling[5]. Furthermore, the clinical trials that have led to approval of SRIs for the treatment of OCD exclude patients with bipolar disorder as a rule. Atypical antipsychotics, which are effective for the treatment of bipolar disorder, have emerged as a therapeutic alternative in refractory OCD, but can be associated with significant side-effects and limited efficacy[6]. Thus, therapeutic options with minor risks have high clinical relevance in this population.

Regarding anticonvulsants, there is a report on 8 refractory OCD patients treated with lamotrigine as add-on to SRIs, with 1 responder[7], and another report of improvement with valproate monotherapy in one patient with OCD[8]. Zink et al.[9] described one patient with schizophrenia that developed obsessive-compulsive symptoms after clozapine was initiated and improved with valproic acid.

We describe two cases of patients with diagnoses of BD and OCD which presented improvement of mood and anxiety symptoms with mood-stabilizers only.

A 36-year-old white woman with previous diagnoses of panic disorder (PD) and recurrent depressive episodes had undergone treatment with antidepressants since 18 years of age, with partial response. Diagnostic evaluation revealed that she later developed episodes of irritable mood, overactivity, racing thought, pressure of speech, decrease need for sleep, paranoid symptoms, buying sprees and anger attacks that lasted up to one month, alternating with depressive episodes, therefore fulfilling the DSM-IV diagnostic criteria for bipolar II disorder. She had obsessive-compulsive disorder since 10 years of age, especially with fear of contamination, repetitive behaviors of excessive cleaning and checking door locks. Under treatment with fluoxetine 20 mg her mood was unstable, with no impact on OCD symptoms.

She started treatment with lamotrigine up to 100mg/d with significant improvement of depressive symptoms, irritability and obsessive-compulsive symptoms. However, panic symptoms increased and paroxetine up to 20 mg was added, triggering a hypomanic episode. Paroxetine was discontinued and divalproex up to 500 mg/d was started. Currently, the patient is on treatment with lamotrigine 100 mg/d and divalproex 500mg/d with improvement of BD, OCD and panic disorder. Her score of Yale-Brown Obsessive-Compulsive Scale (YBOCS) decreased from 46 previous to treatment to 04 after six months.

A 31-year-old white man had bipolar II disorder, with anger attacks, overactivity, racing thoughts in hypomanic episodes that lasted up to one week alternated with episodes of atypical depression. He has family history of BD and reported a switch to mania with venlafaxine in the past. He met DSM-IV criteria for alcohol abuse and OCD. He had obsessive compulsive symptoms since 15 years of age and mood symptoms since 26 years of age. The most prominents symptoms of OCD were repetitive behaviors of checking door locks, electrical outlets and hoarding.

Treatment with divalproex up to 1000mg/d was initiated and after six weeks the patient reported significant improvement of alcohol abuse and obsessive-compulsive symptoms. His YBOCS score declined from 23 previous to treatment to 04.

In agreement with comorbidity studies, some authors have proposed a distinction between bipolar/cyclothymic and unipolar OCD[10,11]. Indeed, the results of Angst et al (2005) suggest that OCD is more comorbid with bipolar spectrum disorders than with unipolar depression and Merikangas et al[2] (2007) have found an odds ratio of 16.7-21.4 for OCD in patients with bipolar I and II disorders, which was the highest odds ratio for a comorbidity in bipolar patients. Considering such level of comorbidity between these disorders, along with treatment difficulties with SRIs in those with bipolar disorder, this is a clearly understudied clinical reality, particularly in terms of treatment. Since the efficacy of SRI has been established in patients with OCD without bipolar disorder comorbidity, their efficacy cannot be assumed for patients with this comorbidity. A logical approach would be to evaluate the efficacy of mood stabilizers alone in these patients, which has not been systematically done to our knowledge. Surprisingly, the few studies that have tested the efficacy of mood stabilizers in OCD have been add-on treatments to SRI and there is only one case report of valproate monotherapy for OCD without bipolar disorder[8] and a report of 2 patients with episodic OCD who responded to lithium monotherapy[12].

It is interesting to note that the onset of OCD predated that of bipolar disorder in both patients, as reported in many cases[13]. However, she responded to valproate and lamotrigine and not to fluoxetine. We have proposed that temperamental or emotional dysregulation may underlie the observed pattern of comorbidities in psychiatry, with particular relevance for some disorders such as OCD, which may be associated with high fear, high anger and/or high control as temperamental traits[14]. Thus, treatment aimed at this

underlying emotional dysregulation could bring about improvement in many comorbidities simultaneously[15].

These present reports on the efficacy of lamotrigine and divalproex without SRIs or atypical antipsychotics in patients with OCD and BD suggests that these drugs may be adequate, at least for some patients. Well-designed controlled trials with mood stabilizers should be conducted in patients with bipolar comorbidities as these conditions are a rule rather than the exception in clinical practice.

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LOW DOSE QUETAPINE FOR PATIENTS WITH DYSREGULATION OF HYPERTHYMIC AND CYCLOTHYMIC TEMPERAMENTS

Luísa W. Bisol[1], MD, Diogo R. Lara[2], MD PhD

1. Departamento de Bioquímica – ICBS – UFRGS, Porto Alegre, Brazil

2. Faculdade de Biociências e Hospital São Lucas, PUCRS, Porto Alegre, Brazil

Corresponding author:

Diogo R. Lara

Faculdade de Biociências – PUCRS

Av. Ipiranga, 6681 Pd 12A

Porto Alegre – RS

Brazil

90619-900

e-mail: drlara@pucrs.br

Fax 55 51 33203612

Short Title: Low dose quetiapine for temperaments

ABSTRACT

Patients with hyperthymic and cyclothymic temperaments often develop symptoms that failed to meet diagnostic criteria for bipolar disorders. These patients can be conceived as having bipolar disorder NOS, a bipolar spectrum disorder, cyclothymic disorder or cluster B personality traits. Here we describe four of these patients with mild to moderate symptoms affecting mood, behavior, emotional reactivity and sleep. Treatment with low dose quetiapine (25-75 mg/day at night) lead to sustained symptom remission. Two of them were on quetiapine monotherapy. Such low doses occupy a minority of D2 and 5-HT2 receptors, which may nevertheless be of therapeutic value in mild cases. Alternatively, other mechanisms more likely to occur at low doses, such as antagonism of H1, alpha(1B)-adrenergic and other serotonin receptors, as well as reduction cortisol secretion, may be involved in the therapeutic efficacy of quetiapine.

KEY WORDS: Quetiapine. Bipolar disorders. Temperament. Cyclothymic disorder.

INTRODUCTION

In clinical settings, patients who look for psychiatric treatment often fail to meet diagnostic criteria for DSM-IV or ICD-10 disorders. According to their symptoms, these patients can only be classified as NOS (not otherwise specified) type of the most similar diagnostic category. An alternative view is to conceive these patients as pertaining to a clinical spectrum of classical conditions, which includes subthreshold symptoms and affective temperaments (Marneros, 2001). In general, these patients have been poorly characterized in clinical, epidemiological and treatment research.

Patients with bipolar spectrum disorders present symptoms that fail to reach the duration criteria of mania-hypomania or number of symptoms (Akiskal and Pinto, 1999). The broad bipolar spectrum is heterogeneous, the boundaries are not yet clear and classification proposals have included other subtypes of 'soft' bipolar disorders (Akiskal, 2005). As a rule, these patients have hyperthymic, cyclothymic or irritable temperaments (Lara et al., 2006). Dysregulation of these temperaments often produce dysphoria, behavioral symptoms, increased emotional reactivity and sleep problems. These patients are sometimes conceived a having a cluster B personality disorder or 'borderline traits'. The closest Axis I diagnosis according to the DSM-IV is cyclothymic disorder, which has nevertheless been poorly studied.

Quetiapine is an atypical antipsychotic recommended for treatment of schizophrenia and bipolar disorders (acute manic and depressive episodes) (Calabrese et al, 2005; Thase et al, 2006). Compared to other atypical antipsychotics, quetiapine has negligible rates of extrapyramidal side effects and differential effects on depressive symptoms. According to the information sheet of Seroquel®, the recommended dose of quetiapine ranges from 150 mg to 750 mg/day. The lowest dose of quetiapine in recent studies on bipolar depression was 300 mg/day. Clinical trials on bipolar disorders include only patients that meet DSM-IV criteria for

bipolar I or II disorder (Calabrese et al., 2005; Thase et al., 2006)**,** neglecting bipolar spectrum patients who are very prevalent in clinical practice (Akiskal et al., 2006).

Treatment regimens for bipolar I disorder are not necessarily applicable for bipolar spectrum disorders. In clinical practice, we often observe that 'soft' patients need 'soft' treatments (i.e. lower doses) that produce symptom improvement, low incidence of side effects and better compliance. Here we describe four of these patients who had marked overall improvement with low dose quetiapine, two of them on monotherapy.

CLINICAL DESCRIPTIONS

Case 1 – A 59-year-old woman described herself as an energetic, funny, talkative and extrovert person, full of thoughts and involved in several activities, which are traits compatible with hyperthymic temperament. In the first meeting, she reported initial insomnia, dysphoria, anxiety, crowded thoughts and skin picking on her face for the last year, without response to trazodone 50 mg/day or lorazepam 1 mg/day. Her daughter has bipolar disorder and her son is addicted to cannabis. She was started on quetiapine 25 mg/day and trazodone was withdrawn. She reported rapid and significant improvement of sleep, less dysphoria and that her 'mind was clear again', but some mood symptoms and skin picking persisted. Quetiapine dose was raised to 50 mg/day and she reported further improvement of sleep, mood and stopped the picking. After three months on 50 mg, she reported mild depressive symptoms, which remitted after increase of quetiapine to 75mg/day. She has remained well for 6 months and reports no side effects.

Case 2 – A 43-year-old woman, owner and CEO of a local food company, complained of emotional sensitivity, impulsivity, dysphoria, non-stop thinking, occasional explosive bouts, anxiety, initial insomnia, unstable energy and a stressful lifestyle (too much work and too little family support and recognition for her efforts). Thyroid hormones were

normal. She fulfilled the DSM-IV criteria for cyclothymic disorder and general anxiety disorder, but not for lifetime hypomanic or depressive episode or for personality disorders. Fifteen years before she had undergone 5 years of psychotherapy and tried lithium, which was not tolerated due to tremor even at low doses (600 mg/day). She then used benzodiazepines for about 10 years and had undergone several attempts with antidepressants, with unsatisfactory results. She had also tried divalproex, which was not tolerated (nausea and headache). At the time of her first visit she was on topiramate 100 mg, with partial response but some memory complaints, and bromazepam 6 mg/day. Lamotrigine was initiated, with some response 1 month later at 50 mg/day and worsening when on 100 mg/day the next month and then suspended also due to her worry on drier skin, despite absence of cutaneous rash. Oxcarbazepine up to 600 mg/day lead to intolerable dizziness and bupropion up to 300 mg/day also failed to produce significant results. Quetiapine was started at 25 mg at night and increased to 50 mg/day three days later. Within a week she reported significant improvement of all emotional symptoms and sleep, and became more resilient to stressful situations. Topiramate and bromazepam were tapered off and withdrawn in two weeks and she reported remission of all her symptoms and marked approval about her mood and behavior by her family members. However, after 4 months of treatment with symptom remission, she complained of weight gain (4 kg) despite walking 5 km 4 times a week and asked for a medication to replace it without weight gain. A trial with aripiprazole up to 10 mg/day was not as efficacious and produced agitation. She lost 3 kg, opted for restarting quetiapine and she rapidly improved again. Metformin 1500 mg/day has helped her to keep her weight at this level.

Case 3 – A 58-year-old woman, working as a lawyer and university associate professor, reported temper outbursts, dysphoria, excessive buying, occasional prodigality, initial insomnia (sometimes with crowded thoughts) and unstable mood since her thirties, which

developed on top of a predominantly hyperthymic temperament. She denied symptoms that were sufficient to fulfill criteria for previous episodes of hypomania or depression, which was confirmed with her husband. She had been on psychotherapy for 4 years, with some benefit for affective relationships. Lamotrigine was initiated and titrated up to 150 mg/day, which lead to more stable mood and fewer days of low energy, but insufficient response of the remaining symptoms after 10 weeks of treatment. Quetiapine was initiated at 25 mg at night and increased to 50 mg after 1 week. She rapidly remitted from all her symptoms and has been well for 4 years on lamotrigine 100 mg/day and quetiapine 50 mg at night, without adverse events.

Case 4 – A 28 year-old actress presented for psychiatric evaluation and was motivated to start psychotherapy for her emotional sensitivity that lead to interpersonal problems about 2 times a month. She also had initial insomnia, sometimes with crowded thoughts, being unable to sleep before 2:00 am. After falling asleep, she usually needed at least 8 hours to feel rested. She denied other symptoms, but reported significant worsening of emotional sensitivity during premenstrual phases. Her affective temperament was predominantly cyclothymic. Besides weekly sessions of psychotherapy, she promptly accepted a trial with quetiapine 25 mg at night. One week later she reported marked improvement of sleep and crowded thoughts at night. She remained on 25 mg for 4 weeks, when she became apprehensive about the opening night of her play and was instructed to increase the dose to 50 mg. She reported feeling better on this dose, which was maintained. Since then, she felt being much more in control (‘in about half of the situations that I would feel angry or hurt, I just manage the situation as everyone else… in the other half, I react but quickly settle down again, which was unusual for me`), less premenstrual dysphoria. She interrupted psychotherapy treatment because she reported having better insight and a clearer view in stressful situations. She has been well for 6 months with no adverse events.

DISCUSSION

Such patients with hyperthymic/irritable/cyclothymic temperaments or cyclothymic disorder who fail to meet DSM-IV criteria for bipolar I/II or personality disorders are a clinical reality. They either have a history of relatively benign cyclothymic, irritable or hyperthymic temperament that starts roughening towards a more symptomatic and dysfunctional dysphoric/cyclothymic state. Their symptoms are nevertheless associated with objective and subjective impairment and require somatic treatment. Due to the common sleep and anxiety problems, such patients are frequently treated with hypnotic or anxiolytic agents, often by non-psychiatrists. This misdirection of treatment is mostly due to the failure to recognize symptoms or traits associated with behavioral/mental activation, such as crowded thoughts, irritability, dysphoria and overactivity. In our clinical experience, these symptoms rarely remit with benzodiazepines, but transient improvement of some symptoms (e.g. sleep, anxiety) often lead do their chronic use. Low dose quetiapine (≤75 mg/day) may produce persistent remission of these dysphoric and agitated states, as in these four patients. Such use of quetiapine seems to be increasing among psychiatrists, but is rarely reported, perhaps due to lack of confidence on the clinical and pharmacological concepts for such use.

The efficacy of quetiapine as an atypical antipsychotic and mood stabilizer is usually attributed to its D2R and 5-HT2R blocking properties. Indeed, relatively high doses of quetiapine (>600 mg/day) produce significant but transient striatal D_2 receptor blockade, which is the putative mechanism for both antimanic and antipsychotic efficacy (Kapur et al., 2000; Gefvert et al., 2001, McIntyre et al. 2007). However, 150-300 mg/day produced ≤11% of striatal D2R occupancy 14 hours after the last dose (Kapur et al., 2000) or around 0% 2 hours after the last dose (Gefvert et al., 2001) using [^{11}C]raclopride as the tracer. Of note, quetiapine was associated with higher D2R occupancy in extrastriatal than striatal regions (17-30% in putamen versus 31-

42% in the amygdala 2 h after 200 mg quetiapine) (Kessler et al., 2006). Quetiapine is a more potent 5-HT2A antagonist (Richelson and Souder, 2000) and occupies 46-73% of these receptors at 300 mg/day (Kapur et al., 2000; Gefvert et al., 2001), which is the dose shown to produce antidepressant effects in bipolar patients (Calabrese et al., 2005; Thase et al., 2006). Other studies showed that the 150 mg/day dose was associated with only 19-22% occupancy 14 hours (Kapur et al., 2000) and ≅40% occupancy two hours (peak level) after quetiapine administration, respectively (Gefvert et al., 2001). These results suggest that the efficacy of 25-75 mg in our patients may be beyond D2R or 5-HT2R blockade. Alternatively, it is possible that low occupancy of these receptors may be sufficient to affect emotion and behavior in patients with mild symptoms.

Other mechanisms of action are likely to contribute to the effects of low dose quetiapine on mood (McIntyre et al, 2007). Quetiapine has high affinity for H1 receptors, which certainly contributes to its effects on sleep, but may exert other effects, such as modulation of cytokines. Interestingly, H1 receptors are down-regulated in depression (Kano et al., 2004) and H1 antagonists have antidepressant-like effects in animal models (Hirano et al., 2006). Quetiapine also has high affinity for alpha1-adrenergic receptors (Richelson and Souder, 2000) and blockade of these receptors reduces behavioral sensitization to amphetamine (Drouin et al., 2002; Salomon et al., 2006), which is model for bipolar disorder and mood cyclicity (Post, 2007). Interestingly, behavioral sensitization occurs mostly in animals with high exploratory behavior, which can be interpreted as a correlate of human hyperthymic temperament (Kaslauckas et al., 2005), mostly due to a higher responsiveness of the noradrenergic system (Alttoa et al., 2007).

Also, the metabolite n-desalkylquetiapine has affinity for the norepinephrine reuptake transporter, the serotonin 5-HT(1A), 5-HT(1E), 5-HT(2A), 5-HT(2B), 5-HT(7) receptors, the

alpha(1B)-adrenergic receptor, and the M(1), M(3), and M(5) muscarinic receptors at 10-100 nM concentrations (Jensen et al., in press).

Quetiapine also influences neuroendocrine parameters. A single dose of 25 mg or 100 mg were equally effective in reducing nocturnal urinary cortisol excretion by around 50% in healthy volunteers (Cohrs et al., 2004). Also, a single dose of quetiapine (50mg) and olanzapine (5 mg), but not haloperidol (3 mg), reduced cortisol and ACTH secretion in healthy volunteers (Cohrs et al., 2006).

In conclusion, low dose quetiapine (25–75 mg) may have therapeutic effects on mood, emotional regulation and sleep in patients with mild to moderate symptoms. These effects may be mediated by mechanisms yet to be clarified, since such low doses are unlikely to substantially occupy D2 and 5-HT2 receptors. Alternatively, patients with mild symptoms may benefit from lower levels of receptor occupancy, including other receptor subtypes, than more severe patients. Further studies are necessary to explore such use of quetiapine in psychiatric settings.

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PARTE IV – CONSIDERAÇÕES FINAIS

Parte 1 – Esquizofrenia e tratamento com flunarizina

O ensaio clínico mostrou que a flunarizina, uma medicação não utilizada anteriormente como antipsicótico, foi eficaz no tratamento de pacientes esquizofrênicos. Outras medicações também têm sido aplicadas com um uso diferente do original, como alopurinol, ômega-3 e hormônio da tireóide no tratamento da esquizofrenia e de outros transtornos mentais (BRUNSTEIN et al., 2005; AKHONDZADEH et al., 2005; BAUER et al., 2002; PARKER et al., 2006). Esses casos sugerem que a busca de novos tratamentos para os transtornos mentais pode ir além da busca de novas moléculas, estendendo-se para novos usos de fármacos conhecidos.

Encontramos na literatura vários relatos de caso de sintomas parkinsonianos após uso prolongado de flunarizina, especialmente em mulheres e idosos. Alguns autores chegam a afirmar que o uso de flunarizina é a principal causa de parkinsonismo induzido por drogas (TEIVE et al., 2003).

Apesar desses relatos oriundos de profissionais da área da neurologia e de evidências de que a flunarizina é um bloqueador dos receptores dopaminérgicos D2, não havia uma investigação consistente do possível efeito antipsicótico desse fármaco.

O artigo apresentado no primeiro capítulo constitui o primeiro ensaio clínico, randomizado, duplo cego, controlado de flunarizina no tratamento de sintomas psicóticos. Os resultados comparáveis ao do grupo controle que utilizou haloperidol, um antipsicótico de primeira geração e com grande eficácia no tratamento dos sintomas positivos da esquizofrenia, são um indício que a flunarizina pode ser uma medicação promissora como antipsicótico.

A semelhança entre os escores de efeitos adversos, um achado diferente do esperado, pode ser explicado pela dosagem adequada de haloperidol que provavelmente produziu um bloqueio dopaminérgico entre 65% e 78%, ideal para obter efeito antipsicótico e com baixa probabilidade de causar efeitos adversos extrapiramidais (KAPUR et al., 2000).

A dose adequada de haloperidol é uma diferença importante entre o ensaio clínico apresentado e os ensaios clínicos publicados que fazem uso de doses mais altas de haloperidol, o que claramente favorece o surgimento de SEP nesse grupo de pacientes. Essa constatação muitas vezes oferece uma limitação na interpretação dos resultados que apontam melhor tolerabilidade aos novos antipsicóticos (HUGENHOLTZ et al., 2006).

A bateria de testes neuropsicológicos não foi capaz de detectar diferenças entre os grupos. Isso se deveu possivelmente ao tamanho limitado da amostra, ao tempo de estudo ou à restrita ação da flunarizina nesses parâmetros.

Os pacientes que participaram da pesquisa eram ambulatoriais e muitos estavam relativamente estáveis na ocasião da seleção. Apesar de ser um fator limitante, é importante ressaltar que somente um paciente em cada grupo precisou ser hospitalizado por exacerbação da esquizofrenia.

Conforme dados de literatura, a taxa de recaída após a retirada do antipsicótico é de 44% em três meses (JESTE et al., 1995). Esse dado possibilita inferir que o tempo de permanência no estudo foi suficiente e que a flunarizina preveniu recaída nesse grupo de pacientes.

Embora não explorado do ponto de vista científico, alguns pacientes seguiram usando flunarizina após o término da pesquisa e se mantiveram estáveis ou até obtiveram maiores

benefícios com o tratamento prolongado. No entanto, esse seguimento não foi documentado sistematicamente.

Por apresentar meia-vida longa e um perfil de efeitos colaterais relativamente favorável, a flunarizina pode ser uma ferramenta no arsenal terapêutico dos pacientes com esquizofrenia e talvez também de outros transtornos mentais, podendo ser especialmente útil naqueles com dificuldade de adesão ao regime medicamentoso.

Com exceção da clozapina, os ensaios clínicos publicados na literatura que comparam a eficácia de antipsicóticos de segunda geração com o haloperidol encontram taxas de resposta similares nos dois grupos com relação aos escores de sintomas positivos da esquizofrenia (HIRSCH et al., 2002; KANE et al., 2002).

Recentemente ensaios clínicos importantes (CATIE e Cost Utility of Latest Antipsychotic Drugs in Schizophrenia Study - CUtLASS 1) que compararam medicações de primeira e segunda gerações não encontraram diferenças significativas entre esses grupos nos parâmetros de eficácia, tolerabilidade e qualidade de vida (LIEBERMAN et al., 2005; JONES et al., 2006).

No entanto, os sintomas da esquizofrenia não se resumem aos sintomas positivos. Os sintomas negativos e cognitivos são os que mais conferem prejuízos ao longo do tempo por serem mais estáveis e difíceis de tratar (KEEFE et al., 2004). As medicações de segunda geração têm outros mecanismos de ação, além do bloqueio dos receptores D_2 da via mesolímbica, que podem conferir eficácia numa maior gama de sintomas da esquizofrenia, bem como maior número de transtornos psiquiátricos, além de não induzirem sintomas negativos secundários (conseqüência dos sintomas positivos, dos efeitos adversos da medicação, da depressão e da privação ambiental) (REMINGTON, 2003).

É também importante ter claro o conceito que os antipsicóticos de segunda geração são um grupo de medicações heterogêneo. Eles possuem diferenças com relação ao mecanismo de ação e à afinidade por receptores. A característica que os torna um grupo é essencialmente a menor (mas não nula) probabilidade de indução de efeitos colaterais extrapiramidais, quando comparados às medicações de primeira geração (FARAH, 2005).

Como perspectivas, o estudo da flunarizina em outras amostras (pacientes com sintomas psicóticos agudos), outros transtornos mentais (transtorno bipolar), bem como a pesquisa da melhor posologia (dose, intervalo entre doses) podem ser objeto de pesquisas futuras.

Parte 2 – Os relatos de caso

Com relação ao segundo capítulo da tese, uma dificuldade encontrada no atendimento de pacientes em clínica psiquiátrica é que muitas vezes os pacientes apresentam quadros atípicos ou sublimiares. Tais condições raramente são objetos de pesquisa (ensaios clínicos) por serem de grande variabilidade.

Nesse sentido, a descrição de casos clínicos é uma tentativa de fomentar a discussão sobre tais situações que são freqüentes e necessitam de mais atenção, na busca de alternativas para o tratamento dessas condições que, de acordo com as classificações oficiais, não são trantornos mentais ou o são, mas são pouco estudados. Nesse sentido, poderemos oferecer tratamento para pessoas com diferentes temperamentos que têm prejuízos e sofrimento com os excessos ou deficiências associados ao temperamento (exemplo: ataques de raiva e temperamento irritável). Um desafio é a tentativa de encontrar as medicações e as doses que possam auxiliar, sem deixar a pessoa “embotada” ou com a sensação de não se reconhecer.

Apesar de serem considerados evidências frágeis, relatos de caso têm importância no cenário científico. Muitas pesquisas provavelmente não teriam progredido sem os questionamentos oriundos de descrições de casos únicos (FARMER, 1999).

Os relatos de caso podem também servir de estímulo para o desenvolvimento de protocolos de pesquisa (estudos abertos, ensaios clínicos randomizados) para esse perfil de pacientes, com o objetivo de oferecer opções de tratamento baseado em evidências.

Como pespectivas, baseado em pesquisa bibliográfica e experiência clínica, foi desenvolvida e validada pelo grupo a Escala Combinada de Temperamentos Afetivo e Emocional que segue sendo aplicada em amostras não clínicas e clínicas e os resultados estão no momento sendo analisados (dados não publicados).

Concluindo, os estudos dessa tese reforçam a idéia de que os psicofármacos podem ser usados eficazmente para tratar transtornos mentais diferentes das suas indicações originais, como é o caso do uso da flunarizina como antipsicótico. Além disso, psicofármacos podem ser prescritos visando à atenuação das desregulações de temperamento dos pacientes. Essa perspectiva sugere que psicofármacos possam ser usados em doses diferentes das indicadas para os transtornos originais, além de poder promover melhora dos quadros psiquiátricos associados à desregulação temperamental.

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ANEXO

TERMO DE CONSENTIMENTO INFORMADO PARA PACIENTES

Nome:
Data de nascimento:____/____/_____
Número:
Médico:

Estudo Flunarizina como Antipsicótico

Antes de participar deste estudo, gostaríamos que você tomasse conhecimento do que ele envolve. Necessitando de outros esclarecimentos sobre o estudo e sobre os seus direitos, você deverá contatar a Dra. Luísa Weber Bisol pelos telefones 3383-1291 ou 9136-3034, a Dra. Miriam Garcia Brunstein pelos telefones 3221-6966 ou 8114-0007 ou Dr. Diogo Rizzato Lara pelos telefones 3331-8130 ou 8121-9187.

Qual o objetivo da pesquisa?

Com este estudo estamos testando um novo remédio para o tratamento da esquizofrenia. A Flunarizina tem características químicas semelhantes a medicamentos modernos usados para o tratamento de esquizofrenia (antipsicóticos atípicos ou de segunda geração) e já demonstrou ser eficaz em alguns pacientes, mas até o momento não existem estudos científicos desse novo uso da flunarizina. O objetivo da pesquisa é comparar a eficácia da flunarizina com haloperidol e verificar se a flunarizina é uma nova alternativa para o tratamento da esquizofrenia

Quais são os riscos em participar?

O flunarizina é usado há muito tempo em pacientes com vertigem, enxaqueca, problemas de labirinto e doenças da circulação cerebral.

Os efeitos colaterais são pouco comuns e podem ser aumento do sono, cansaço, aumento da fome e ganho de peso. Raramente pode ocorrer azia, enjôo, vômitos, boca seca, fraqueza, dor muscular e alergia de pele. Com o uso prolongado e em dose altas pode levar a alterações de movimentos semelhantes ao parkinson (tremores, rigidez muscular, lentificação dos movimentos, dificuldades para caminhar) ou inquietação que melhoram com o uso de biperideno (Akineton®) ou outra medicação antiparkinsoniana.

Os efeitos colaterais do uso de haloperidol que é a medicação padrão para tratamento de esquizofrenia são semelhantes às da flunarizina, mas tendem a ocorrer com maior freqüência. Também melhoram com uso de biperideno ou com a parada do remédio.

Como será o estudo ?

Serão selecionados 70 pacientes com diagnóstico de esquizofrenia ou de transtorno esquizoafetivo (segundo critérios diagnósticos do DSM-IV), entre 18 e 55 anos, que serão sorteados para receber flunarizina ou haloperidol. Antes de iniciar o estudo os pacientes farão

exames de sangue, peso, testes de funções neurocognitivas e, então, será retirada a medicação em uso. Essas avaliações serão repetidas no final do estudo. O estudo acontecerá por 12 semanas. Após a triagem e início do tratamento, o paciente terá consultas nas semanas 1, 3, 6, 9 e 12. Todos pacientes reberão 2 cápsulas para tomar à noite. Após uma semana, a medicação será avaliada, se preciso ajustada, e também poderão ser usados biperideno ou prometazina se for necessário. As cápsulas dos dois grupos serão iguais, assim o paciente e o médico não saberão a ordem dos tratamentos, para evitar que as avaliações sejam tendenciosas. Apenas um outro médico que não estará envolvido diretamente na avaliação do paciente saberá essa informação

Em cada consulta, o paciente e o responsável serão entrevistados pelas médicas do estudo: Dra. Miriam ou Dra. Luísa.

A coleta de sangue (dois tubos pequenos) é um procedimento corriqueiro e de baixíssimo risco e que não compromete em nada a saúde do paciente. O exame será feito com material esterilizado e descartável por profissionais da área de saúde com competência técnica.

Os testes de avaliação cognitiva estão divididos em dois grandes grupos: os de funções frontais (atenção difusa, escolha de categorias e atenção focal) e os de memória. Os testes do primeiro grupo são *Trial Making Test*, *Wisconsin Card Sorting Test*, *Stroop Test* e alguns subtestes da bateria WAIS-R (*Number Span*, *Block Design* e *Digit Symbol*), enquanto os do segundo são *Logical Memory* e *Visual Reproductions*, ambos da bateria WMS-R. A testagem cognitiva tem duração estimada de 40 minutos, variando conforme o *timing* do testando, e será feita pelo Psicólogo Ricardo Vígolo de Oliveira ou pela psicóloga Gisele Paz.

Itens importantes

Sua participação neste estudo é voluntária. O paciente e o responsável têm a liberdade de desistir do estudo a qualquer momento, sem fornecer um motivo, assim como pedir maiores informações sobre o estudo e o procedimento a ser feito.

O que eu ganho com este estudo?

Sua colaboração neste estudo visa acrescentar para o conhecimento científico sobre o tratamento da esquizofrenia. Além disso, a curto e médio prazos o paciente pode se beneficiar com tratamento em estudo.

Quais são os meus direitos?

Os pesquisadores do serviço de psiquiatria e os representantes das autoridades competentes da Biosegurança podem precisar examinar os seus registros a fim de verificar as informações para o objetivo deste estudo. No entanto, os seus registros médicos serão sempre tratados confidencialmente.

Os resultados deste estudo poderão ser publicados em um jornal científico ou submetido à autoridade de medicamento competente, mas você não será identificado por nome.

1. Concordo total e voluntariamente em fazer parte deste estudo; tenho mais de 18 anos.
2. Recebi uma explicação completa do objetivo do estudo, dos procedimentos envolvidos e o que se espera de mim. O médico me explicou os possíveis problemas que podem surgir em consequência da minha participação neste estudo.
3. Informei o médico sobre medicamentos que estou tomando.
4. Concordo em cooperar inteiramente com o médico supervisor.

5. Estou ciente de que tenho total liberdade de desistir do estudo a qualquer momento e que esta desistência não irá, de forma alguma, afetar meu tratamento ou administração médica futura.
6. Estou ciente de que a informação nos meus registros médicos é essencial para a avaliação dos resultados do estudo. Concordo em liberar esta informação sob o entendimento de que ela será tratada confidencialmente.
7. Estou ciente de que não serei referido por nome em qualquer relatório relacionado a este estudo. Da minha parte, não devo restringir, de forma alguma, os resultados que possam surgir neste estudo.

Paciente:**Responsável**:
Assinatura:_____Assinatura:_____
Nome:_____ Nome:_____
Data:_____ Data: _____

Médico:**Testemunha**:
Assinatura:_____Assinatura:_____
Nome:_____ Nome:_____
Data:_____ Data: _____

Nome:

Desfecho e medicações	**S 0** / /	**S !** / /	**S 3** / /	**S 6** / /	**S 9** / /	**S 12** / /
PANSS	X		X	X	X	X
ESRS	X	X	X	X	X	X
Testes cognitivos	X					X
Prolactina	X					X
Peso	X					X
Medicação	x	x	x	x	x	

Dra. Luísa Weber Bisol fone: 9136-3034
Dra Miriam Brunstein fone: 8114-0007