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FARMACOTERAPIA POTENCIALMENTE INAPROPRIADA PARA O IDOSO À LUZ DA LITERATURA CIENTÍFICA

ANA PATRÍCIA ALVES LIMA SANTOS

SÃO CRISTÓVÃO-SE

FEVEREIRO 2014

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ANA PATRÍCIA ALVES LIMA SANTOS

Exame de qualificação apresentado ao Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade Federal de Sergipe para obtenção do título de Mestre em Ciências Farmacêuticas. Área de concentração: Assistência Farmacêutica.

Orientador: Prof. Dr. Ângelo Roberto Antoniolli

Coorientador: Prof. Dr. Divaldo Pereira de Lyra Junior

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FARMACOTERAPIA POTENCIALMENTE INAPROPRIADA PARA O IDOSO À LUZ DA LITERATURA CIENTÍFICA

Dissertação apresentada ao Núcleo de Pós-Graduação em Ciências Farmacêuticas da Universidade Federal de Sergipe como requisito parcial à obtenção do grau de Mestre em Ciências Farmacêuticas

Aprovada em: _____/_____/_____

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RESUMO

SANTOS APAL. Farmacoterapia potencialmente inapropriada para o idoso à luz da literatura científica. Dissertação do Mestrado em Ciências Farmacêuticas, Universidade Federal de Sergipe, 2013.

INTRODUÇÃO. A maior predisposição a doenças crônicas e consequente uso de vários medicamentos nos idosos, aumenta a chances do uso de farmacoterapia potencialmente inapropriada ao idoso (FPII). Os efeitos prejudiciais da FPII impulsionaram profissionais a desenvolverem métodos para identificar padrões de prescrição de FPII em diferentes países e cenários de prática. OBJETIVO. Avaliar a FPII à luz da literatura científica. METODOLOGIA. O estudo foi estruturado em três etapas. A primeira correspondeu a uma revisão sistemática a fim de identificar quais são os instrumentos de avaliação de FPII utilizados pelo mundo, bem como investigar quais são os termos utilizados para se referir a FPII. A segunda etapa correspondeu a uma revisão sistemática que objetivou avaliar o rigor metodológico dos estudos que avaliam FPII. A terceira etapa correspondeu a uma metanálise que avaliou a heterogeneidade de estudos que avaliam a associação de FPII com os fatores de risco; idade, sexo e polifarmácia. RESULTADOS. O instrumento mais utilizado pela literatura é o proposto por Beers. Foram encontrados mais de 50 termos para se referir a FPII. Dos estudos analisados, nenhum cumpriu todos os itens propostos pela Strengthening the Reporting of Observational Studies in Epidemiology. Apenas a polifarmácia teve associação positiva com o uso de FPII. CONCLUSÃO. Estes resultados devem orientar futuras pesquisas nesta área, oferecendo uma abordagem mais completa sobre os aspectos relacionados com o uso de medicamentos por esta população específica.

PALAVRAS-CHAVE: Idoso, utilização de medicamentos, farmacoterapia inapropriada para o idoso.

ABSTRACT

SANTOS APAL. Potential inappropriate drug therapy in the light of the scientific literature**.** Dissertação do Mestrado em Ciências Farmacêuticas, Universidade Federal de Sergipe, 2013.

INTRODUCTION. The greater predisposition to chronic diseases and consequent use of various medications in the elderly increases the chances of the use of potential inappropriate drug therapy (PIDT). The damaging effects of PIDT boosted professionals to develop methods to identify patterns of prescription PIDT in different countries and practice scenarios. PURPOSE Assess FPII the light of the scientific literature. METHODOLOGY. The study was structured in three stages. The first corresponded to a systematic review to identify what are the assessment tools used by the world FPII and investigate what are the terms used to refer to FPII. The second stage corresponded to a systematic review aimed to assess the methodological rigor of studies evaluating FPII. The third step corresponds to a meta-analysis that evaluated the association FPII with risk factors, age, sex and polypharmacy. RESULTS. The instrument most commonly used in the literature is the one proposed by Beers. Found more than 50 terms to refer to PIDT. Of the studies reviewed, none fulfilled all items proposed by the Strengthening the Reporting of Observational Studies in Epidemiology. Only polypharmacy had a positive association with the use of FPII. CONCLUSION. These findings should guide future research in this area, offering a more complete approach on aspects related to the use of medications for this specific population.

KEYWORDS: Elderly, medication use, potential inappropriate drug therapy (PIDT).

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INTRODUÇÃO

1. INTRODUÇÃO

O envelhecimento da população é um fenômeno mundial. Segundo a Organização das Nações Unidas (ONU), nos próximos anos o número de pessoas com mais de 60 anos de idade será três vezes maior do que o atual. Os idosos representarão um quarto da população mundial projetada, ou seja, cerca de dois bilhões de indivíduos(United Nations, 2011)

O avanço da idade cronológica traz alterações fisiológicas e patológicas, o que eleva a predisposição a doenças crônicas e consequente uso de vários medicamentos. Na medida em que o uso de medicamentos aumenta, as chances de ter um evento indesejado relacionado ao uso se elevam, principalmente quando se prescreve algum tipo de farmacoterapia potencialmente inapropriada ao idoso (FPII). Dessa forma, a prescrição de medicamento para essa faixa etária constitui um desafio (Ribeiroet al.,2005;Gallagher et al.,2007;Soares et al., 2011).

Alguns estudos têm debatido em todo o mundo que muitos dos padrões utilizados na prescrição da farmacoterapia dos idosos são inapropriados. (Iyeret al.,2006; Laroche et al.,2007;Albert et al., 2010).De acordo com Beers e colaboradores (1991), um medicamento é considerado potencialmente inadequado quando seus riscos superam seus benefícios.A identificação de FPII é realizada por meio de instrumentos implícitos e explícitos desenvolvidas por especialistas (Ribeiro et al., 2005). Existem diversos critérios que avaliam FPII, dentre os quais o mais utilizado foi o elaborado por Beers. Este tem sido usado principalmente para examinar a prevalência e as tendências na prescrição de FPII(Gallagheret al.,2007).

A cada atualização dos critérios de Beers,novas práticas educativas são implementadas para que os profissionais da saúde prescrevam de maneira mais segura (Martin et al.,2013).Nos últimos anos, outros instrumentos como oScreening Tool of Older Persons`potentially inappropiate prescriptions(STOPP) e o Screening Tool to Alert doctors to Right Treatment (START)também vem sendo extensivamente utilizados. De acordo com estudos recentes, esses critérios possuem confiabilidade e boa sensibilidade

para detectar FPII(Gallagheret al.,2008; Montero et al.,2008;Gallagher et al., 2009).

Com o aumento da taxa de prescrição de FPII em todo o mundo, cresce a morbimortalidade relacionada a medicamentos(Laroche et al.,2007;Albert et al.,2010). De acordo com Bakken et al. (2012), FPII é prevalente em idosos hospitalizados e segundo Albert et al. (2010), o risco de hospitalização aumenta em uma relação dose-resposta de acordo com o número de FPII.

Somado aos eventos adversos, a alta taxa de FPII aumenta os gastos em saúde.De Smet et al. (2007) afirmaram que prevençãodeFPIIs pode resultar naeconomiade orçamentos em saúde. Embora o controle de gastossejaum elemento importante, aanálise da farmacoterapia do idoso deve priorizar o acesso ao medicamento adequado e a segurança do paciente(Cahir et al.,2010).

Exitem diversos instrumentos que vem sendo usados no mundo inteiro para avaliar as FPII, mas há poucas evidências científicas a respeito da sua validade (Marriott, Stehlik, 2012).Aliado a isso há grande variabilidade de resultados e qualidade de estudos publicados na área, o que torna a estimativa de valores de prevalência e incidência de FPII nos mais diversos cenários um desafio.Assim, mais estudos de alto grau de evidência como revisões sistemáticas e metanálises devem ser elaborados, uma vez que o envelhecimento é um fenômeno mundial e a consolidação desse tipo de conhecimento se faz preciso(Cano,Rozenfeld, 2009;Pintor-Marmolet al.,2012).

As revisões sistemáticas são úteis para integrar as informações de um conjunto de estudos realizados separadamente sobre determinada terapêutica/intervenção, que podem apresentar resultados conflitantese/ou coincidentes, bem como identificar temas que necessitamde evidência, auxiliando na orientação para investigaçõesfuturas. Além disso, podem ser empregadas para responder questões relativas a testes diagnósticos, fatores prognósticos e epidemiológicos. São baseadas emrevisão da literatura focando uma pergunta claramentedefinida e para a qual são identificados,avaliados e selecionados artigos com o objetivode sintetizar evidências relevantes.(Linde, Willich, 2003; Fuchs, Paim, 2010).

As metanálises são um tipo de revisão sistemática que adicionalmente usam métodos estatísticos para combinar quantitativamente e agregar resultados de pesquisas individuais.As revisões sistemáticas de ensaios clínicosrandomizados são mais frequentemente publicadas,permitindo avaliar eficácia de intervençõese, com maior número de participantes e deeventos, aumentando o poder estatístico paradetectar diferenças entre tratamentos. (Fuchs, Paim, 2010)

Já as metanálisesde estudos observacionais são mais propensasa vieses devido às características dos delineamentos observacionais.Contudo, hipóteses etiológicas não podemser testadas em delineamentos experimentais.Ainda que fatores de risco individualmente representembaixo risco, não seria possível alocarindivíduos para exposição associada a riscocom o objetivo de avaliar a incidência de doença.Mesmo exposições associadas a baixo riscoabsoluto de doença são capazes de determinarimpacto em saúde pública se parte da populaçãoestiver exposta ao fator de risco, o que justifica a realização de metanálises de estudos observacionais.(Strom, 2006; Papanikolaouet al., 2006;Fuchs, Paim, 2010).

Embora esses tipos de estudos tenham alto grau de evidência científica e a temática da FPII ser muito explorada na literatura, há poucos estudos que avaliem a utilização de termos para se referir a FPII, o rigor metodológico dos artigos publicados na área e a associação de FPII com fatores de riscos. Logo, é necessário realizar investigações que discutam esses temas que podem contribuir para assistência em saúde e proporcionar maior segurança aos idosos que utilizam medicamentos.

Estrutura desta Dissertação

No que se refere à execução desta Dissertação, o percurso empreendido para a sua concepção começou no início do mestrado acadêmico em Ciências Farmacêuticas. Este surgiu como uma das linhas ramos de pesquisas do Laboratório de Ensino e Pesquisa em Farmácia Social (LEPFS). O LEPFS surgiu em meados de 2007, na Universidade Federal de Sergipe (UFS) e desde então vem desenvolvendo estudos voltados para pesquisa, ensino e extensão na área da Farmácia Social.

Este trabalho foi iniciado com o objetivo de estudar os padrões mundiais de prescrições da farmacoterapia potencialmente inapropriada para o idoso. Apresente Dissertação teve a orientação dos professores doutores Ângelo Roberto Antoniolli e Divaldo Pereira de Lyra Júnior, além da colaboração do professor do Departamento de Medicina, Dr Marcos Antônio Prado Nunes, dos doutorandos Daniel Tenório da Silva, Carina Carvalho Silvestre, Genival Araújodos Santos Juniore da aluna de iniciação científica Vanessa Alves da Conceição.

Ante ao exposto, esta Dissertação foi estruturada em quatro partes: a primeira é a Fundamentação teórica. A segunda parte, por sua vez, é o Capítulo 1 que aborda as tendências mundiais de uso de instrumentos para avaliar a potencial inapropriação da farmacoterapia prescrita para o idoso, bem como os termos utilizados pra se referir a inapropriação. A terceira é o capítulo 2 que avaliou os estudos que avaliavam FPII, bem como o cumprimento dos itens propostos pela “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)”. Na última, o capítulo 3, foi realizada uma metanálise que objetiva avaliar a heterogeneidade dos estudos que estimam a associação entre o uso de FPII e fatores de risco (idade, sexo e polifarmácia). O Capítulo 1 e 2 serão submetidos à revista *Drug and Aging* e o capítulo 3 será submetido à revista *Plos One*.

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FUNDAMENTAÇÃO TEÓRICA

2. FUNDAMENTAÇÃO TEÓRICA

2.1. Envelhecimento da população

Uma das maiores mudanças sociais trazidas pela melhoria dos padrões de vida da população é o envelhecimento (Thakur et al.,2013). O número de pessoas com mais de 60 anos no planeta vai aumentar em quase 200 milhões nos próximos dez anos.Os avanços da Medicina e as melhoras nas condições gerais de vida da população repercutem no sentido de elevar a média de vida do brasileiro de 45,5 anos de idade, em 1940, para cerca de 73 anos, em 2008 e em 2050 alcançará o patamar de cerca de 81 anos; basicamente o mesmo nível atual da Islândia (82 anos), Hong Kong, China (82 anos) e Japão (83 anos)(Laroche et al., 2007;IBGE, 2008).Este panorama mundial é o contribuinte universal para as etiologias de declínio metabólico e doenças relacionadas, incluindo Diabetes mellitus tipo 2 e doença cardiovasculares(Barzilai et al.,2012).

Na população geriátrica, a prevalência de problemas de saúde é elevada. Com o envelhecimento há um conjunto de alterações fisiológicas que podem diminuir o estado funcional de diversos órgãos heterogeneamente e progressivamente. Dentre as quais, têm-se: alterações celulares, hormonais, termorreguladoras, cutâneas, musculares,posturais e do equilíbrio, funções nervosas, cardiovascular, gastrointestinais, órgãos dos sentidos, paladar e olfato, visão, audição,sono, dentre outras. Essas alterações favorecem maior incidência de doenças agudas ou crônicas e, por conseguinte, um considerável aumento do uso de medicamentos. Além disso, decrepitude de órgãos como fígado e rins pode influenciar no efeito e toxicidade de alguns medicamentos.(Mann et al., 1988)

2.2. Uso de medicamentos pelo idoso

As alterações fisiopatológicas associadas ao envelhecimento podem modificar a resposta ao uso medicamentos e reduzir a segurança ao paciente. O declínio dessas funções fisiológicas se traduz por alterações em alguns parâmetros farmacodinâmicos e farmacocinéticos. Assim, a sensibilidade de fármacos varia em função do número e da capacidade de ligação aos

receptores, que diminuem com o avanço da idade. Em consequência, pode ocorrer redução da frequência máxima e arritmias cardíacas, hipotensão postural, dentre outros problemas (Azevedo et al.,2007).Ademais, o envelhecimento provocaalterações da superfície de absorção, no volume de distribuição de fármacos, do fluxo sanguíneo hepático, além do fluxo renal e filtração glomerular(Katzung, 2009).

Em função das peculiaridades comuns ao envelhecimento e o alto índice de doenças crônicas que atinge cerca de 80% dos idosos aumenta o consumo de medicamentos. Segundo a literatura, os idosos utilizam em média de dois a seis medicamentos prescritos e de um a três sem prescrição, o que pode gerar polifarmácia(Michocki e Lamy, 1988;Routledgeet al.,2004; Flores e Benvegnú, 2008).Assim, a polifarmácia que pode ser definida como o uso de múltiplos medicamentos concomitantemente, torna-se prática comum nessa faixa etária, mas apesar de ser necessária em alguns casos pode aumentar o risco de interações medicamentosas, baixa adesão à farmacoterapia e reações adversas a medicamentos (RAM)(Hovstadius et al.,2010).

De modo geral, as interações medicamentosas são um tipo particularmente importante de eventos adversos a medicamentos, porque são muitas vezes previsíveis com base em estudos clínicos anteriores. (Sepehriet al.,2012) Por outro lado, vários estudos realizados apontam que a população idosa possui elevada chance de hospitalização causada por interações medicamentosas. (Costa, 1991; Lindbladet al.,2005; Cruciol-Souza, Thomson, 2006)De acordo com Pasina et al. (2013) existe associação positiva entre mortalidade e interação medicamentosa em pacientes com pelo menos duas interações potencialmente graves. Assim, a monitorização cuidadosa é importante para minimizar o risco e danos.

No caso das RAMs, asmesmas causam quatro vezes mais hospitalizações entre os idosos que entre os adultos, como altos índices de morbimortalidade relacionada ao uso de medicamentos. (Onderet al.,2002; McLean, Couteur, 2004) Essas reações podem ser caracterizadas como respostas a um medicamento que seja prejudicial, não intencional e que ocorre em doses normalmente utilizadas no ser humano. Enquanto algumas reações

adversas aos medicamentos são imprevisíveis, tais como as idiossincrasias, muitos outrosefeitos colaterais ou hipersensibilidades alérgicas podem ser antecipados e evitados. Diante desses problemas, a prescrição de medicamentos para idosos deve ser cautelosa e priorizar a segurança dos pacientes. (WHO, 1972)

2.3. Prescrição de medicamentos para idosos

Na prática clínica, os prescritores devem avaliar as alterações fisiológicas anteriormente citadas e os medicamentos que o paciente faz uso (Terrel et al.,2006).Nesse sentido, o mesmo deve considerar as mudanças na depuração hepática do medicamento, meia-vida, biodisponibilidade e volume de distribuição. Por isso, aumenta a complexidade para prescrever determinados fármacos, pois as chances de RAMs nessa faixa etária se elevam, o que pode aumentar o abandono de diversos tratamentos(Schwartz, 1999; Shelton et al.,2000).Além disso, outras barreiras podem dificultar a adesão à farmacoterapia, dentre as quais, destacam-se: a prescrição de esquemas terapêuticos complexos, tratamento de doenças assintomáticas, perda da capacidade cognitiva e aspectos socioeconômicos (Osterberg, Blaschke, 2005).

Na tentativa de reduzir a morbimortalidade relacionada aos medicamentos, diversas estratégias para otimizar as prescrições dos idosos têm sido desenvolvidos instrumentos e métodos que avaliem problemas farmacoterapêuticos.De acordo com Beers et al. (1991), um medicamento pode ser inapropriado devido a três fatores: uso sem necessidade ou usoexcessivo; utilizaçãoinadequada de dose, esquema posológico ou duração terapêutica ou por omissão deum medicamento que o paciente necessite (subutilização) (Shea et al., 2004).

2.4. Instrumentos que avaliam a farmacoterapia de idosos

Quanto aos métodos que avaliam a adequação farmacoterapêutica para idosos, os mesmos são categorizados em implícitos (ex. Medication Reduction Project), explícitos (ex. critérios de Beers), ou implícito-explícitos (ex. Medication Appropriateness Index). Os primeiros se caracterizam por revisões

terapêuticas específicas para cada indivíduo, considerando as práticas adequadas nas revisões de literatura médica sobre as doenças específicas apresentadas pelos pacientes. Entretanto, não têm a preocupação de definir ou padronizar critérios e necessitam de uma estrutura de revisão baseada em consenso.

Um dos métodos implícitos encontrado na literatura é o Medication Reduction Project (MEDRED). Este instrumento foi desenvolvido nos Estados Unidos, em 1993, para abordar questões de polifarmácia em idosos. Consiste em apresentações educativas e avaliações da farmacoterapia realizadas por um farmacêutico especializado em geriatria. Além disso, o projeto possui cinco metas; reduzir o número de medicamentos utilizados; ajustar as doses; aumentar a adesão ao tratamento; identificar os impactos sociais, funcionais e econômicos da farmacoterapia; e incentivar o uso de alternativas não farmacológicas quando clinicamente indicado (Schraderet al. 1996; Ribeiro et al. 2005).

Os explícitos, por sua vez, são mais utilizados pela literatura e limitados no que se refere à adequação clínica, geralmente são baseados em métodos de consenso e incluem a utilização de listas, contendo medicamentos a serem evitados por idosos (Ribeiro et al. 2005) (Quadro 1).Inúmeros são os instrumentos explícitos disponibilizados na literatura, a exemplo doscritérios de Beers et al.(1991, 1997, 2003, 2012), McLeod criteria, Improved Prescribing in the Elderly Tool (IPET),Zhan criteria, French list, START/STOPP, Assessing Care of Vulnerable Elders (ACOVE), entre outros.

Os critérios de Beers foram desenvolvidos em 1991, utilizando a técnica de Delphi modificada, com a criação de uma lista de 30 medicamentos que devem ser evitados em idosos de instituições de longa permanência, independentemente do diagnóstico, a dose ea frequência do uso de medicamentos. Em 2003, o critério foi modicido por Fick e colaboradores que consideraram 48 medicamentos ou classes de medicamentos inadequados, dividindo-os em dois: 1) medicamentos ou classes que deveriam ser evitados em idosos, independentemente do diagnóstico ou da condição clínica, devido ao alto risco de efeitos colaterais e pela existência de outros fármacos mais

seguros; 2) medicamentos ou classes que não deveriam ser usados em determinadas circunstâncias clínicas (Gorzoniet al., 2008; Clyne et al., 2013).

De acordo com Terrel et al., 2006, os medicamentos potencialmente inapropriados para idosos são ciclobenzaprina prescrito para espasmo muscular ou dor, diazepam, difenidramina para sintomas alérgicos, alergias sazonais, dermatite de contato, indometacina para gota aguda, prometazina para náusea, vômito e insônia, entre outros.

Na versão de 2012 dos Critérios de Beers, foram incluídos 53 medicamentos, ou classes de medicamentos, divididos em três categorias: medicamentos potencialmente inadequados e classes que devem ser evitados em idosos (indistintamente); medicamentos potencialmente inadequados e classes que devem ser evitadas em idosos com certas doenças e síndromes; e, por fim, medicamentos que devem ser usados com cautela em idosos. Esta atualização tem muita força, por utilizar uma abordagem baseada em evidências, segundo as normas do *Institute of Medicine*, além de formar uma parceria destinada a atualizar regularmente os Critérios. A aplicação cuidadosa dos critérios permitirá; (a) melhorar o monitoramento do uso de medicamentos, (b) aplicar prescrições eletrônicas em tempo real e intervenções para reduzir os eventos adversos a medicamentos em idosos, e (c) melhorar os resultados do cuidado prestado aos pacientes.(American Geriatrics Society, 2012)

Devido às limitações das versões iniciais dos critérios de Beers, diversos instrumemtos foram desenvolvidos em diferentes países com o objetivo de complementá-las. No Canadá, McLeod et al. (1997) desenvolveram uma lista, usando a técnica de Delphi modificado, de 71 práticas de prescrição para idosos, pois critérios previamente desenvolvidos não eram aplicáveis aos idosos canadenses. Para cada nível clínico é utilizada uma escala de um (não significativo) a quatro (muito importante). Com relação ao intrumentos, as práticas na prescrição são divididas em três categorias: medicamentos em geral contraindicados para pessoas idosas, interações fármaco-doença e interações fármaco-fármaco.

Ainda no Canadá, em 2000, foi desenvolvido os critérios IPET que consite em uma lista baseada nos critérios desenvolvidos por McLeod et al.

1997 e teve como objetivo criar uma breve e fácil ferramenta de triagem para detectar farmacoterapia potencialmente inapropiada em idosos(FPII). Embora a vantagem do IPET, o mesmo recebeu atenção limitada mundialmente por causa de seu âmbito restrito e inclusão de critérios obsoletos.(Levy et al., 2010). Critérios desenvolvidos no Japão e Itália são semelhantes aos critérios de Beers, com adaptações discretas feitas para atender às necessidades de cada um destes países. (Akazawaet al., 2010; Maio et al., 2010)

Nos Estados Unidos, Zhan et al. (2001) modificaram oscritérios de Beerspara um estudodo uso de medicamentospotencialmente inapropriadosemidosos não institucionalizados.Na França, Laroche e colaboradores (2007) desenvolveram uma lista pelo método Delphi, elaboradas por especialistas de várias partes da França e de diferentes origens (geriatras, farmacêuticos, clínicos gerais, farmacoepidemiologista). Por fim, foi criada uma lista de 36 critérios aplicáveis a idosos franceses de 75 anos de idade ou mais.

Na Irlanda, os critérios de STOPP/START foram criados com os seguintes objetivos: (i) capturar exemplos comuns e importantes de farmacoterapia potencialmente inapropriada; (ii) ser organizados de acordo com os sistemas fisiológicos, seguindo o exemplo da maioria dos formulários de medicamentos; (iii) dar especial atenção aos medicamentos que afetam negativamente os idosos em risco de quedas; (iv) dar especial atenção ao consumo de opióides em idosos; (v) destacar a duplicidade terapêutica; (vi) tratar os erros de omissão de prescrição em pessoas idosas; (vii) os critérios devem representar o ponto de vista de consenso de um painel de especialistas na prescrição em pessoas idosas.(O'Mahony et al., 2010)

Com esses princípios, o primeiro projeto de lista de possíveis erros de prescrição foi produzido em 2003. Em 2006, os critérios STOPP/START foram validados usando a metodologia Delphi. Para a elaboração do instrumento, foi realizado um consenso de 18 especialistas em geriatria, farmacologia clínica, farmácia clínica, psiquiatria e primary care. O objetivo principal dos instrumentos é permitir que clínicos examinem a farmacoterapia facilmente dentro da prática clínica diária. O STOPP é dividido em 10 categorias, que vão desde os sistemas cardiovascular, respiratório e endócrino a duplicidade

terapêutica e medicamentos que favorecem as quedas. O START é dividida em 6 categorias de omissão de prescrição, também de acordo com os sistemas fisiológicos, incluindo cardiovascular, respiratório e sistema nervoso central. (O'Reilly et al., 2004; Shelton et al.,2010; Gallagher, Byrne, 2008)

O instrumento ACOVE contêm 43 indicadores de qualidade relativos ao atendimento farmacológico. Durante a realização desse projeto foi desenvolvido um conjunto de indicadores de qualidade explícitos para avaliar o atendimento prestado aos idosos vulneráveis. O sistema concentra-se em processos de atendimento dentro dos domínios da prevenção, diagnóstico, tratamento e acompanhamento. Além disso, abrange todo o espectro de atendimento contido em 22 condições que são importantes no cuidado aos pacientes idosos. Os métodos incluíram revisões sistemáticas da literatura e opiniões de especialistas. (Higashiet al., 2004; Wenger, Shekelle, 2001).

Outros instrumentos, além dos citados, foram desenvolvidos em todo o mundo, como o Australian criteria na Austrália, o Phadke criteria na Índia,NorwegianGeneral Pratice (NORGEP) criteria no Canadá, National Taiwan University Hospital (NTUH)-modified criteria no Taiwan, PRISCUS list na Alemanha, Winit-Watjana criteria na Tailândia, entre outros. (Rognstad et al., 2009; Holt et al., 2010; Chang et al., 2011García-Gollarte et al.,2012; Singh 2012)

No tocante aos critério implícito-explícitos, o mais utilizado na literatura é o criado por Hanlon em 1992, o Medication Appropriateness Index (MAI). Esse instrumento foi elaborado como parte de um ensaio clínico para avaliação de serviços em saúde nos Estados Unidos por um geriatra e um farmacêutico clínico mede a adequação da prescrição para os pacientes idosos, por meio de dez critérios para cada medicamento prescrito: indicação (sinal, sintoma, doença ou condição para prescrição), efetividade (produção de resultado benéfico), dose (total de medicamentos tomados em 24 horas), administração (instruções para uso correto de um medicamento), comodidade/praticidade (capacidade de ser usado ou colocado em prática), interações medicamento-medicamento (efeito que a administração de um medicamento tem em outro, geralmente prejudicial), interação medicamento-doença (efeito que um

medicamento tem em uma doença ou condição pré-existente, geralmente prejudicial), duplicidade terapêutica (prescrição não benéfica ou arriscada de dois ou mais medicamentos de mesma classe farmacológica ou química), duração (período de tempo do tratamento) e custo (custo de um medicamento em comparação com outros agentes de igual eficácia e segurança). (Quinalha, Correr, 2010)

Para cada elemento foram estabelecidas definições operacionais e instruções para a avaliação e são classificados em medicamento adequado, marginalmente apropriado ou inapropriado. O suporte é fornecido por meio de definições e instruções explícitas. O MAI tem sido utilizado em estudos observacionais e de intervenção. Sua viabilidade, validade de conteúdo, validade preditiva e confiabilidade têm sido demonstradas em ambientes ambulatoriais e é um método com instruções operacionais fáceis e úteis para revisar um grande número de medicamentos utilizados pelos pacientes idosos. Contudo, não teve sua validade externa atestada devido à ausência de um padrão de comparação. Além disso, possui algumas desvantagens, como a de não incluir em sua escala a presença de RAM (exceto aquelas provocadas por interações medicamento-medicamento e medicamento-doença), devido, segundo o autor, à existência de algoritmos próprios para isso; não incluir a presença de problema de saúde não tratado, qualidade de vida e não adesão ao tratamento; além de o tempo despendido para revisar cada medicamento ser de aproximadamente dez minutos, o que pode impossibilitar sua aplicação em locais muito movimentados. (Ribeiro et al., 2005; Spinewine et al., 2006; Quinalha,Correr, 2010;)

Em 1993, também nos Estados Unidos, Lipton e colaboradores desenvolveram um instrumento com característicasimplícitas-explícitas. Esse critério foi desenvolvido e foi criado por um painel de médicos e farmacêuticos clínicos que definiram seis categorias de problemas de prescrição e um sistema de escore que classifica a magnitude desse problema. O método possui vantagens, como o instrumento não ser fármaco-específico, permitindo a avaliação do fármaco no contexto da condição clínica de cada indivíduo. Entretanto, possui desvantagens, como a demora da aplicação do instrumento, pois cada fármaco é avaliado individualmente. Outro aspecto destacado pelos

autores como desvantagem do instrumento é a estreita faixa dos escores obtidos, o que pode gerar dúvidas quanto categoria avaliada. (Ribeiro et al., 2005)

Possibilitar a segurança da farmacoterapia do idoso é importante para a sua qualidade de vida. Para tanto, a pesquisa e estudos sobre o assunto é fundamental para nortear as condutas médicas, além da aplicação de diferentes instrumentos que contemplam diferentes medicamentos. (Quadro 1) Dessa forma, a demanda por qualidade máxima do cuidado em saúde, combinada com a necessidade de uso racional de recursos, tem contribuído para aumentar a pressão sobre os profissionais da área no sentido de assegurar a implantação de uma prática baseada em evidências científicas. (Bennett, Bennett, 2000)

Quadro1. Exemplos de medicamentos potencialmente inapropriados para os idosos

Critério	Exemplo de medicamentos
Beers	• Independente do diagnóstico: meperidina (alta gravidade) • Considerando o diagnóstico: úlceras gástricas ou duodenais com AINEs e ácido acetilsalicílico (> 325 mg / dia); coxibes excluídos
McLeod (1997)	• Prescrição de reserpina para tratar a hipertensão • Prescrição de benzodiazepínicos de meia-vidalonga para tratar agitação na demência
French list	• O uso concomitante de 2 ou mais AINEs • Bloqueadores dos canais de cálcio: nifedipina, nicardipina, reserpina • Urapidil, prazosina para incontinência urinária
STOPP	• Digoxina na dose a longo prazo> 125 mg / dia, com comprometimento da função renal • Bloqueadores dos canais de cálcio com constipação crônica
START	• A Varfarina deve ser prescrita na presença de fibrilação atrial crônica • A suplementação de cálcio e vitamina D deve ser prescrita em pacientes com osteoporose conhecida

2.5. Saúde baseada em evidências

As ações dos profissionais de saúde devem ser embasadas nas melhores evidências disponíveis, a fim de minimizar as possibilidades de eventos indesejáveis.Segundo a literatura, as metanálises apresentam o mais alto nível de evidência cientifica, seguidas das revisões sistemáticas. (Atallah, Castro, 1998;Wannmacher, Fuchs, 2000; Watson et al., 2002)

As revisões sistemáticas e metanálises têm sido progressivamente mais utilizadas, substituindo revisões extensivas, pois sumarizam evidências e possibilitam a tomada de decisões clínicas. Essas revisões baseiam-se na revisão da literatura focando uma pergunta claramente definida e para a qual são identificados, avaliados e selecionados artigos com o objetivo de sintetizar evidências relevantes. (Fuchs, Paim, 2010) Entre as principais características da revisão sistemática estão: fontes de busca abrangentes, seleção dos estudos primários sob critérios aplicados uniformemente e avaliação criteriosa da amostra. (Lopes, Fracolli, 2008)

A metanálise é o método estatístico utilizado na revisão sistemática para integrar os resultados dos estudos incluídos. Para que estudos possam ser combinados por meio de uma metanálise, é necessário definir quais resultados serão combinados. Quando a variabilidade nos resultados é grande, os artigos são considerados heterogêneos. Na presença de heterogeneidade, análises alternativas como metanálise em subgrupos e metaregressão podem ser consideradas para explicar a variabilidade entre os grupos. (Rodrigues, Ziegelmann, 2010)

O caminho metodológico resumido da revisão sistemática e metanálise está representado pela Figura 1. A fim de realizar um estudo robusto, todas as etapas devem ser realizadas rigorosamente.As diretrizes da declaração Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) e Colaboração Cochranefornecem importantes e confiáveis instruções para o desenvolvimento de uma revisão sistemáticade qualidade. (Moher et al., 2009; Higgins, Green, 2011)

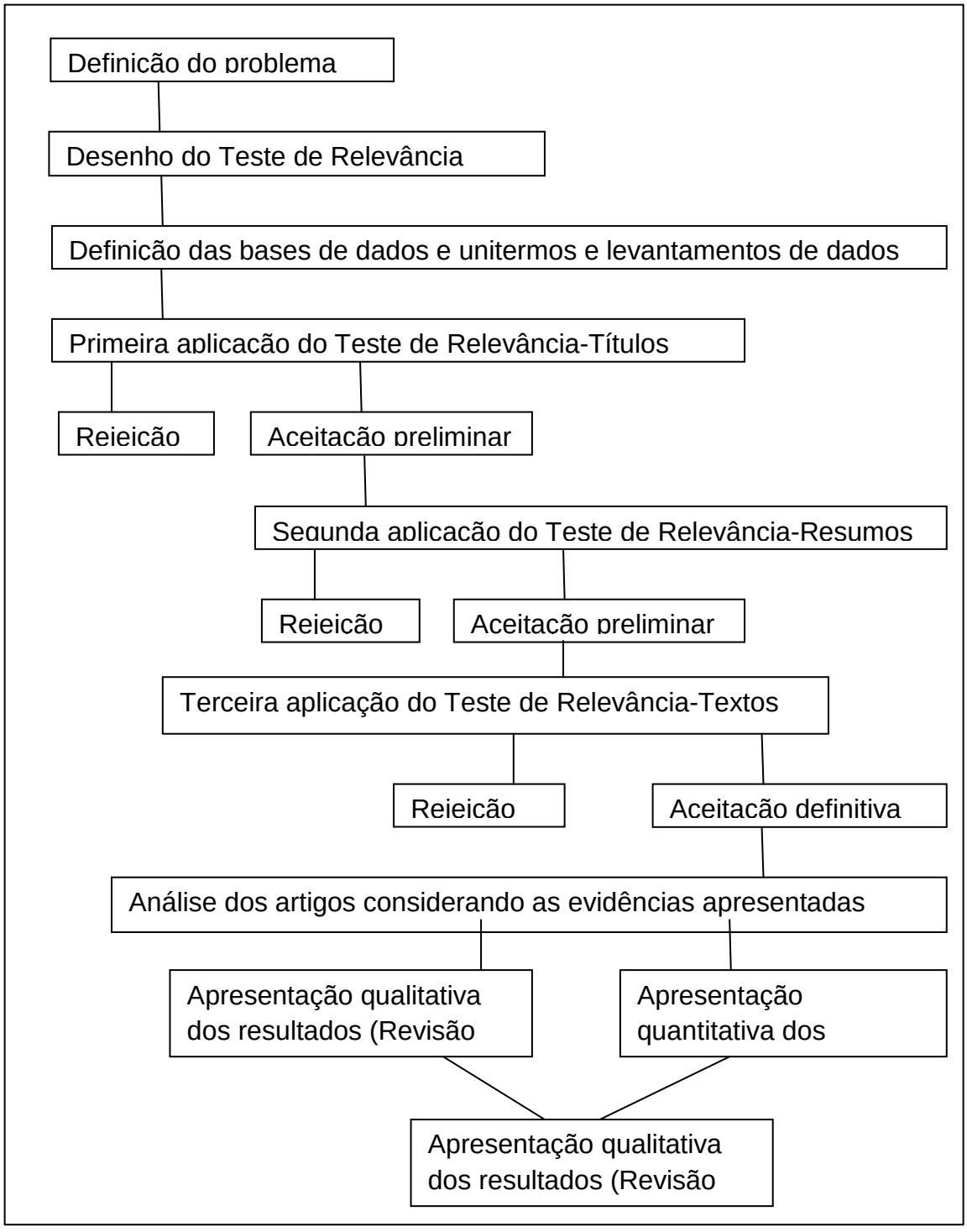

Figura1-Diagrama de Fluxo para a elaboração de uma revisão sistemática e metanálise (Adaptado de Muñoz et al,2002).

O teste de Relevância consiste em um questionário em que são definidos os critérios de inclusão e exclusão, constituídos por perguntas que geram uma resposta afirmativa ou negativa. Questões mal formuladas levam a

decisões obscuras sobre o que deve ou não ser incluído na revisão. (Laroche et al.,2007; Clyne et al.,2013)

Metanálises de ensaios clínicos randomizados são mais comuns. Contudo,em muitas situações, ensaios clínicos randomizados não são viáveis e somente dados de estudos observacionais estão disponíveis. Estudos sobre fatores de risco geralmente não podem ser randomizados, pois se referem a características ou práticas humanas e a exposição a fatores de risco prejudiciais é antiético. Apesar das metanálises de ensaios randomizados serem preferíveis, o número de metanálises de estudos observacionais cresceu nas ultimas décadas. (Badgettet al., 1997)

As metanálises de estudos observacionais apresentam desafios particulares devido aos vieses inerentes desse tipo de estudo, ainda que, pode representar uma ferramenta para ajudar a compreender e quantificar as fontes de variabilidade nos resultados entre os estudos. Além disso, uma meta-análise realizada com cuidado pode revelar áreas que necessitam de mais pesquisas.(Ioannidis, Lau, 1999)

Nos últimos anos muitas revisões têm sido publicadas sobre FPII, contudo mais pesquisas de alto grau de evidência devem ser realizadas a fim de consolidar essa área.

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OBJETIVOS

3 OBJETIVOS

3.1 OBJETIVO GERAL

Avaliar a FPII à luz da literatura científica.

3.2 OBJETIVOS ESPECÍFICOS

- Avaliar quais as tendências sobre os termos eos instrumentos utilizados para detectar os FPIIem diferentes cenários de prática (Capítulo 1).
- Avaliar o rigor metodológico dos estudos que avaliam FPII (Capítulo 2).
- Comparar os estudos que avaliam a associação entre fatores de risco e o uso da FPII (Capítulo 3).

CAPÍTULO 1

Conceptualizing and measuring potential inappropriate drug therapy tools: a review of published studies

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ABSTRACT

Elderly people are the principle consumers of prescription drugs. The more medication used by the patient, the greater the likelihood of being subjected to potential inappropriate drug therapy (PIDT).The PIDT is measured in the literature using implicit and explicit tools. The purpose of the review was to assess the use of tools to detect PIDT in various studies, and to determine which terms are used to refer to PIDT in practice. A systematic review was carried out, according to the following steps: (1) identification, in which studies were selected from different combinations of the descriptors: “aged,” “elderly,” “inappropriate prescribing,” and “drug utilization,” in three different languages in the Pubmed, Scielo, Scopus, and Web of Science databases; (2) the papers that satisfied the inclusion criteria for data extraction were carefully examined according to the tools used, and terms that referred to PIDT. At the end of the selection process, 119 of the articles complied with the specified criteria. As for the PIDT evaluation criteria used by the studies, 27.7% used two criteria. Of the 27 evaluation criteria identified, the Beers criteria were used by 82.3% of the studies. As for the terms used to refer PIDT, more than 35 different terms were found. The review showed that the number of articles in the literature aimed at evaluating PIDT using implicit and explicit tools is increasing.

INTRODUCTION

Currently, almost 65% of the world population lives in countries where life expectancy is over 60 years [1]. Estimates show that 15.6% of the population will reach this age group in 2050, a population four times that of the young population[2]. However, elderly people are the principle users of prescription drugs. This increased use of medications is associated with age-related diseases [3].

Among this population, a specific set of physiological alterations decrease the functioning of various organs.The progressive reduction in functioning is reflected at the pharmacokinetic and pharmacodynamic level.These aspects should be considered when elderly people are treated with pharmacotherapy, since the pathophysiological alterations may alter their response to drugs, with the possible reduction of safety [4]. The problem is potentiated with polypharmacy, when more than five medications are prescribed. According to Beers et al. 2005, the greater the amount of drugs used by the elderly patient, the greater the likelihood of the patient being subjected to potentially inappropriate drug therapy (PIDT) for this age group, thus raising the risk of adverse reactions. [5]

Potentially inappropriate medication prescriptions can be defined as medication for which the risks outweigh the benefits.[6] The use of these medications in older people can result in increased morbidity, hospitalizations, and mortality. [7] According to Bakken et al. 2008, PIDT were prevalent among older people acutely admitted to hospital.[8] The PIDT is measured in the literature using implicit and explicit tools.The first tool is characterized by the specific therapeutic revisions of each individual, and does not establish evaluation criteria.The second tool is based on consensus methods, and includes the use of lists containing drugs to be avoided by elderly people. [9]

The use of these medications is directly related to practical problems. In Ireland, for example, 36% of those aged 70 years or over received at least one PIDT, with an associated expenditure of over

€45 million.[10,11] In a study conducted in the United States, Albert et al. (2010) found that the risk of hospitalization increased in a dose-response relationship, according to the number of PIDTs. [12,13]

Based on the problem, the theme requires a comprehensive and detailed analysis of the use of PIDTs.The purpose of the review was to assess the use of tools to detect PIDT, and identify the terms that refer to PIDT in various practical scenarios.

METHODS

A review of the scientific literature was performed to identify studies involving PIDT. The LILACS, PubMed, Scopus, and Web of Science databases were reviewed (until Jan 21, 2013). The search strategy included the keyword terms, in English:“aged,” “elderly,” “inappropriate prescribing,” and “drug utilization”; in Spanish: “anciano,” “utilización de medicamentos,” and “prescripción inadecuada”; and, in Portuguese “idoso,” “medicamento inapropriado,” “medicamento inadequado,” and “uso de medicamento,” in various combinations. The research strategies were implemented according to the protocols of each database. The terms used were defined from queries in the National Library of Medicine's controlled vocabulary thesaurus (MeSH). It consists of sets of terms naming descriptors in a hierarchical structure that permits searching at various levels of specificity. In addition to the MeSH terms, other non-standard terms were used to extend the search strategy.The study design followed the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)

The subsequent screening process was performed in three stages (title, abstract, and full-text screening) by two researchers; when a disagreement occurred, a third researcher analyzed and judged the discrepancy. The measure of agreement between the two reviewers, defined as Cohen’s kappa (k) was calculated with confidence interval of 95%. Titles and abstracts were compared to the following predefined inclusion criteria to determine the relevance of the theme: (i) the study involves the use of PIDT (ii) the use of a tool to evaluate PIDT.

The excluded studies were: (i) reviews and editorials, (ii) studies not written in English, Portuguese or Spanish, (iii) studies that did not provide the full text, (iv) studies evaluating only one or two classes of drugs, and (v) studies evaluating PIDT in only one or two diseases. A researcher (A.P.A.L.S.) made an initial selection, excluding the titles that did not meet the inclusion criteria.

The papers that satisfied the inclusion criteria for data extraction were carefully examined regarding the following variables:

• Tools used, and

• Terms used to refer to PIDT.

RESULTS

From the combinations of keywords, 8.610 articles were found.A prior assessment conducted by one of the evaluators excluded 7.372 articles that did not meet the inclusion criteria. Of the remaining 1.238 articles, 484 were repeated in the databases searched.Thus, 754 titles were considered potentially relevant.Of these, 359 were excluded for not meeting the inclusion criteria, leaving 395 articles to be evaluated by analysis of the abstracts. A further 44 abstracts were not available, so only 351 abstracts

were read and evaluated.Of these, 144 were excluded for not meeting the inclusion criteria. Thus, 207 articles remained. At first, 76 articles had no free access. However, 50 articles were later retrieved by the program of bibliographic commutation of the Brazilian Institute of Science and Technology (IBICT-Switch). Of the articles manually assessed, 62 did not meet the inclusion criteria. At the end of the selection process, only 119 articles met the specific inclusion criteria. [3, 11, 13-15, 17-24,32-36, 40-43, 46-48, 57-65,67-148]

Figure 1 shows the progressive selection, the number of articles, and the reasons for exclusion at each step. The degree of agreement among evaluators was moderate for the titles (κ_1 = 0.479), and substantial for abstracts (κ_2 = 0.647). At all stages, the intervention of a third evaluator was necessary to resolve disagreements between the two primary researchers.

As for the PIDT evaluation criteria for used by the studies, 27.7% used two criteria, 9.2% used three, and only one study used six criteria.Of the 27 evaluation criteria found in this review, the Beers criteria were used by 82.3% of the studies.Of these, 51% were criteria updated in 2003 and three used the Beers criteria, but did not define the year of publication.Four articles developed their own criteria for evaluating PIDT.

Regarding the terms used to refer to the potential inadequacy of pharmacotherapy in elderly people, over 57 different terms were recorded (8 in Spanish, 2 in Portuguese and 47 in English), with approximately 86% of the articles using two or more terms throughout the manuscript. (Table 1)

DISCUSSION

The number of studies describing the method as “intervention studies” or “clinical trials” accounted for only 9.2% of the sample of this review.In these articles, the tools were used to evaluate the intervention of the health professional, proving to be an important support tool for evaluating the adequacy of pharmacotherapy in elderly patients [14- 24]. The tool most commonly used for these interventions studies was the Medication Appropriateness Index (MAI). This can be explained by the fact that this tool performs a detailed evaluation for each prescribed drug, which generates greater confidence in making the correct decision [25].

Regarding the use of criteria for evaluating the PIDT, the most widely used tools were the Beers criteria, followed by the STOPP criteria and the MAI. The Beers criteria have been used extensively to examine medication use in older adults. These criteria, or modifications thereof, have been used to study prescriptions in nursing homes, assisted living, and board and care facilities, as well as for homebound older adults, and community-dwelling elderly patients.The preference for the use of the Beers criteria may be related to the fact that the instrument is a pioneer in the analysis of pharmacotherapy for elderly patients.Additionally, to apply these criteria, hardly any of the patient’s physiological information is required, and its application is faster than other methods, such as the MAI. [26]

The MAI is a prime example of the group of tools that uses implicit-explict criteria. The instrument allows the assessment of a specific drug in the context of the clinical condition of the patient, since each drug is individually evaluated. [25] However, its application can be time consuming, which limits its use in some situations. [27]Unlike the criteria developed by Hanlon et al. 1992, Beers and STOPP are part of the group of explicit criteria. The STOPP criteria can serve as a triage tool to categorize and

prioritize patients according to the severity of their conditions. [25,27]The main limitation for the use of explicit lists is the lack of consideration for the clinical conditions of an individual patient. [28]

Accordingly, tools that use explicit criteria should not replace the clinical judgment of the physician or health care professional because, under specific circumstances, and based on individual assessment, the use of potentially inappropriate drug therapy can be justified. [29,30] Therefore, they do not represent an absolute contraindication, but indicate that these drugs should be used rarely.Nevertheless, the use of these methods has several advantages, among them the practicality of the application, as well as serving as a preventative warning for the identification of vulnerable groups to the occurrence of drug-related problems. [28]

Some studies in this review used more than one criterion, or more than one version of the same criterion, simultaneously. Many studies have adapted explicit criteria, mainly because of the availability of medicines in the country where the study was conducted. These adaptations are explained in part by the use of administrative databases containing no details about the drugs or how they are used. In addition, extrapolations are made to countries other than where the criterion originated, where dosages may not be the same, and prescription habits may be different from the method's country of origin. Additionally, adaptations included drugs with a pharmacological profile similar to those mentioned in the criterion and available in the study country. These facts indicate the difficulties involved in extrapolating criteria from the country of origin to other countries, emphasizing the importance of developing tools appropriate for the location in which they will be used. [31]

In comparison, the STOPP criteria are generally able to detect or identify more potentially inappropriate medications than the Beers criteria. In the article by Mandavi et al., the Beers criteria identified 286 potentially inappropriate prescriptions in 18.3% (243) patients, while the matching PIDT rate identified by STOPP was 21.4% (284) in 346 prescriptions with potentially inappropriate drug therapies (PIDT). [17] This article supports other studies included in the review [20, 32-36] that, when comparing the criteria, show that the STOPP criterion identifies more PIDT than the Beers.This is because STOPP contains 33 PIDT instances not found in Beers. [37]

A conducted a study in 2011 in two hospitals in Taiwan, comparing the practicability of six different PIDT criteria in geriatric outpatients who used multiple medications. The criteria were developed in the USA, Canada, France, Norway, Ireland, and Thailand. Criteria with a higher number of statements and a higher percentage of local market/institutional drug availability tended to detect more PIDT. The number of statements also had a positive correlation with prevalence of PIDT, except in the Rancourt criteria. Many authors consider the strategy of using more than one method comprehensive and constructive, allowing a more complete picture of the studied phenomenon. [38, 39]

Four studies found in this review have developed a criterion for the evaluation of pharmacotherapy in the elderly [3, 40- 42].Only one study [40] does not explain in detail how the criteria was prepared and/or validated. A study[41] reached a consensus using a Nominal Group Technique, and others two[3, 42] developed an explicit criteria list for PIDT based on the literature, and validated by a modified Delphi method. The Rancourt criteria were developted[42]and also were used by Chang et al. 2010. [43] The careful development of new instruments that assess PIDT is an essential strategy for adapting assessment

tools to the practical scenario or country of application, since the range of medicines available in a particular country is different from others. [44]

The wide variability in the potentially inappropriate prescription of pharmacotherapy in the elderly population may be due to differences in evaluation criteria, sample sizes, and study designs used. The observational studies included in the review were mostly cross-sectional and cohort, and showed a positive association between PIDT and the occurrence of adverse events, increasing age, and female gender.However, this association was not unanimous. Maio et al.[45], for example, noted that women had less chance of receiving a PIDT.

Some articles included in this study [5, 20, 32,46- 48], evaluated, in addition to PIDT, the omission of prescriptions using the Screening Tool to Alert doctors to Right Treatment (START).This is a vital alert tool to health professionals, since it alerts them to drugs that cannot be prescribed in certain clinical conditions. [49]Thus, the combination of tools supports the broad evaluation of pharmacotherapy, to allow the evaluation of a larger number of indicators of potential problems related to the use of the medication.[50]

In this study, various expressions were found to refer to the term PIDT.Homes et al. 2009, claim that the definition and standardization of these expressions are necessary to enable the reader to interpret the results and relate them to the context. [51] Moreover, the creation of new terms should be accompanied by concepts facilitating their differentiation from the existing terms. [52, 53]

Regarding the terms used to refer PIDT within the broad field of clinical treatment, potentially inappropriate pharmacotherapy for the elderly population is primarily conceptualized in three ways: first,as potentially inappropriate medication and thus potentially inadequate by itself; second, the drug's suitability depends on the clinical condition of the patient; and finally, drug-drug interactions and pharmacological disease, for example, are taken into account to determine the potential inappropriateness [54-56].This distinction is important and should be clear in the studies, since the application of each one requires different settings.The latest definition, for example, is applied to the implicit methods of PIDT evaluation, and the first two are applied in the explicit methods.

The Medical Subject Headings (MeSH) lists the term as "inappropriate prescribing" and defines it as "the practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist." This definition was not followed in most studies that used the term, as they were not aimed at evaluating drug administration process, but at evaluating the prescription itself. [3,11,40,41,57-67] However, in some countries the term "prescribing" relates to prescription.Thus, it is necessary for the article to clearly define what is being evaluated for the method to be reproducible and results comparable.[5]

As for the MeSH term "inappropriate prescribing," its definition favors some of the tools created to evaluate PIDT, since it emphasizes the potential for inappropriate treatment.Thus, in an attempt develop a comprehensive definition, we use the term potentially inappropriate drug therapy, because the definition of drug therapy is more comprehensive and, in accordance with the MeSH, it means "the use of drugs to treat a disease or its symptoms."

AGENDA FOR FUTURE STUDIES

The focus of current studies on PIDT emphasizes the importance of conducting a meta-analysis of observational studies to verify whether the variables analyzed in most studies are, in fact, risk factors for the use of PIDT.Furthermore, the development of specific tools for each country is necessary, because the range of available drugs differs from one country to anotherIn addition to evaluating the instruments, it is important to assess the quality of studies to ensure the robustness and reliability of the results.Finally, more detailed studies to define the correct term for PIDT is vital, as no consensus currently exists.

STRENGHTS AND LIMITATIONS

Strengths were that this review was the first study that conceptualizes and discusses terms that refer to PIDT. Also, it makes a comprehensive assessment of the instruments used by the world literature. On the other side, this study had certain limitations. The use of English, Portuguese and Spanish keywords, as well as the limited number of keywords can omit valuable publications; this limitation is common to systematic review articles. Other key words like potential inappropriate drug therapy were not used.Furthermore, database restriction and the search strategy may have excluded critical studies that were not published in the data sources used. The exclusion criteria used in the study may have also excluded relevant studies and some articles are difficult to access. Moreover, studies that obtained negative results may not have been published.

CONCLUSION

This review allowed us to verify that the number of articles aimed at evaluating PIDT through implicit and explicit tools is increasing.The Beers criteria were used most often in practical scenarios, but other tools such as STOPP had been widely used, because it is considered to be more complete by some authors.These findings do suggest positive potential in terms of patient safety.However, this review found that there is still no consensus to refer to PIDT, with over 50 different terms currently in use.Further research is necessary to minimize the differences between study results.

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Figure 1 –Study selection process

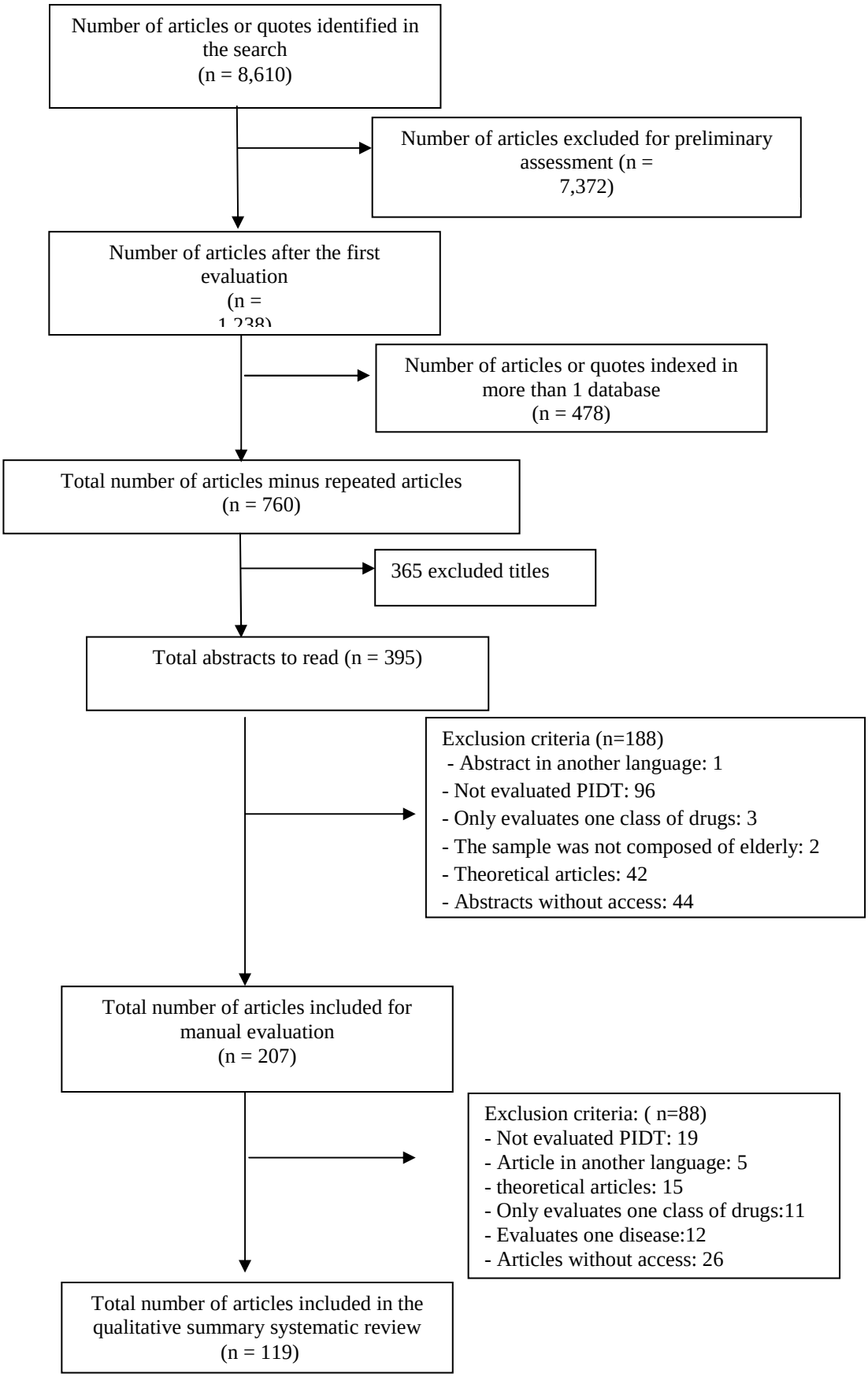

Table 1.Tools used by articles

Tools	References
Adaptation of Beers criteria, 1991	23
Adaptation of Beers, 2003	143/146/148
Assessing Care of Vulnerable Elders (ACOVE)	18
Association with the Nursing Home Surveyors' Interpretive Guidelines	92
Australian criteria	46
Beers (year not clear)	47
Beers 1991	99/141
Beers 1993	92
Beers 1997	18/57/58/63/81/83/88/92/95/98/99/106/107/108/110/112/113/114/116/117/119/137/138/139/145/ 147
Beers 2003	13/16/17/20/32/33/34/41/45/60/61/63/64/67/68/70/71/72/74/75/76/77/78/80/82/84/85/86/87/90/94/96/97/98/99/102/104/105/107/110/115/123/124/127/ 128/129/130/131/132/135/137/145
British National Formulary	15
French list	43/69/83/101/ 103
Improved Prescribing in the Elderly Tool (IPET)	67/128
MAI modified	22/ 66/118
McLeod criteria	64/78/ 107
Medication Appopriateness Index (MAI)	14/18/19/20/21/24/68/93/ 122/123/128
Phadke Criteria	60
Rancourt criteria	42/43
STOPP START	11/ 20/32/33/34/43/46/47/48/ 59/ 129
The Norwegian General Practice (NORGEP) criteria	43/ 126
Zhan Criteria	16/78/85/89/91/ 110/120/138/ 139/ 144

Table2- Terms used by articles

Terms	References
Appropriate Medication	3
Appropriate Prescribing	32
Appropriateness of medications	20/75/121
Appropriateness of Prescribing	18/21/60/84/122
Drug Therapy Problems (DTP)	33
Drugs Considered Potentially Inappropriate for Elders	16
Drugs to be Avoided in the Elderly (DAE)	133
Inappropriate Drug Prescribing	17/ 119/137
Inappropriate Drug Prescriptions	40/ 132
Inappropriate Drug Use	70/ 99
Inappropriate Drugs	46/ 57/58/ 81/ 90/ 97/ 98/ 99/ 105/ 108/ 112/ 114/ 115/ 117/ 140/ 144
Inappropriate Medication	15/23/41/42/64/66/67/70/75/77/87/90/97/102/106/107/108/109/112/117/118/ 123/131/139/144/148
Inappropriate MedicationPrescribing	94/ 103/ 139
Inappropriate Medication Use	70/ 76
Inappropriate medicines	14/ 98
Inappropriate Prescription Medication	147

Table2- Terms used by articles (continuation)

Terms	References
Inappropriate Prescribed	78
Inappropriate Prescribing	3/11/15/22/24/32/40/41/48/57/58/60/61/63/64/66/67/82/103/105/123/125/126/ 128/ /135/141
Inappropriate Prescriptions	40/46/85/91
Inappropriate Use of Medicines	18
Medicación Crónica Inapropiada	129
Medicación Inadecuada	80
Medicación potencialmente inapropiada en ancianos	13/80
Medicamentos potencialmente inapropriados	34
Medication Appropriateness	21/93/118/122/128
Medications Inappropriate	24
Pharmacological Inappropriateness	3
Pharmacologically Inappropriate Prescriptions	3
Potential Drug Therapy Problems (PDTP)	33/145
Potentially Harmful Medications	88

Table2- Terms used by articles (continuation)

Terms	References
Potentially Inappropiate Drug Prescribing	113/ 137/ 138/ 139
Potentially Inappropriate Drug	57/83/ 96/ 97/ 99/101/104/106/113/116
Potentially InappropriateDrug Therapy Prescribing	146
Potentially Inappropriate Prescription	42/46/91
Potentially inappropriate drug prescription	69/132
Potentially inappropriate drug Use	72
Potentially Inappropriate MedicationPrescribing	17/41/45
Potentially inappropriate medications (PIM)	15/16/20/36/42/43/ 45/48/ 69/ 70/ 71/ 72/ 76/ 77/ 79/ 81/ 82/ 83/ 84/ 85/ 86/ 87/ 88/ 92/94/ 95/ 96/ 101/ 102/ 107/ 110/ 116/ 120/ 121/124/125/126/130/131/135/143/144/145/147
Potentially inappropriate medications Use	72
Potentially Inappropriate Medicines(PIMs)	32/36/61
Potentially inappropriate Prescribed	78
Potentially Inappropriate Prescribing	11/20/32/45 47/ 59/104/110/115/119/ 124/128/ 133/ 138/ 139/ 141/ 143/ 146/ 148
Potentially Inappropriate Prescribing in the Elderly (PIPE)	89/ 63
Prescribing appropriateness	78/ 20
Prescribing Inappropriateness	93
Prescrição de medicamentos inapropriados (PMI)	68

Table2- Terms used by articles (continuation)

Terms	References
Prescripción Inadecuada (PI)	129
Prescripción inapropiada de medicamentos	13
Prescripciones Inapropiadas	127
Prescripciones Potencialmente Inapropiadas (PPI)	127
Rational (appropriate) Prescribing	60
Uso inadecuado medicamentos	34

CAPÍTULO 2

Analysis of the studies quality that evaluate potential inappropriate drug therapy

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ABSTRACT

In elderly people, the increased predisposition to chronic diseases and consequent use of various medications increases the chances of using a potential inappropriate drug therapy (PIDT).The purpose of this review was to analyze the researches that uses tools to analyze PIDT through the STROBE initiative. A systematic review was carried out according to the following steps: identification of studies, in which studies were selected from different combinations of the descriptors: "aged," "elderly," "inappropriate prescribing," "drug utilization," in three different languages in different databases; the papers that satisfied the inclusion criteria for data extraction were examined regarding the following variables: country, sample size, duration, type of study, practice scenario, limitations of the studies, and fulfillment of the items proposed by the STROBE initiative for observational studies. At the end of the selection

process, 119 of the articles complied with the specific criteria. The U.S. was the country with the highest number of publications in this area. The samples observed were heterogeneous, ranging from patient to database samples. The majority of the studies were cross-sectional. As for the study practice scenario, the most frequently used were hospitals or outpatient clinics. No article complied fully with the STROBE criteria. This review shows that PIDT is being studied primarily in developed countries, which reinforces the need for further studies in developing countries. These findings should guide future research in this subject area, providing a more complete approach on aspects related to the use of medications by this specific population.

INTRODUCTION

The aging process produces physiological and pathological alterations that increase the predisposition to chronic diseases and consequent use of various medications.This increased consumption of medication raises the odds of the elderly population using five or more drugs, defined as polypharmacy, and increases the occurrence of problems related to the use of medication [1,2]. For this reason, pharmacotherapy in the elderly is a challenge, especially if potential inappropriate drug therapy (PIDT) is prescribed, because it increases health risks [3].

According to Beers and collaborators (1991), a medication is considered potentially inappropriate when its risks outweigh its benefits [4].Notably, elderly patients consume three times more medications that young adults in industrialized countries [4]. According to Brekke et al. 10% to 20% of hospital admissions among elderly people are due to the use of PIDT [5].This is because elderly persons using PIDT are 1.8 to 1.9 times more likely to be hospitalized. [6]

Additionally, there is a global debate that many of the standards used in the prescription of pharmacotherapy in older people are inappropriate[7]. For example, a study conducted in the south of Ireland with 1.329 patients over 65 years of age, with an average of five drugs per patient, identified 632 prescriptions containing PIDT [6].Laroche et al. showed that the incidence of damage caused by medication was 20.4% among patients with PIDT, compared to 16.4% for patients who use only medications appropriate for the elderly. [8]

Concern regarding the harmful effects of the use of medication by the elderly led health professionals such as pharmacists and physicians to develop and implement various methods and tools to identify PIDT prescription patterns [2].Therefore, the adequacy of these techniques should be evaluated by explicit and implicit methods, and the tools validated to reduce PIDT prescription. [7,9]

Some revisions debate these instruments but there are few published systematic reviews assessing the quality of studies using tools that evaluate PIDT in various practice scenarios [10,11The purpose of this review was to analyze the researches that uses toolsto assess PIDT through theStrengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative.

METHODS

To evaluate the variables of this article, data was collected from “Conceptualizing and measuring potential inappropriate drug therapy tools: a review of published studies”, described later.

A review of the scientific literature was performed to identify studies involving inappropriate prescriptions for elderly patients. The LILACS, PubMed, Scopus, and Web of Science databases were reviewed (up to Jan, 2013). The search strategy included the following keyword terms, in English:“aged,” “elderly,” “inappropriate prescribing,” and “drug utilization”; in Spanish “anciano,” “utilización de medicamentos,” and “prescripción inadecuada”; and in Portuguese: “idoso,” “medicamento inapropriado,” “medicamento inadequado,” and “uso de medicamento,”in various combinations. The research strategies were adapted according to the protocols of each database. The keywords were defined using the National Library of Medicine's controlled vocabulary thesaurus (MeSH). It consists of sets of descriptors, arranged in a hierarchical structure that permits searching at various levels of specificity.In addition to the MeSH terms, other non-standard terms have been used to expand the search strategy.The study design followed the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)

The subsequent screening process was performed in three stages (title, abstract, and full text screening) by two researchers (A.P.A.L.S. and D.T.S); when there was disagreement, a third researcher (D.P.L.J) analyzed and judged the discrepancy. The measure of agreement between the two reviewers, defined as Cohen’s kappa (κ) was calculated with confidence interval of 95%. Titles and abstracts were compared, using the following predefined inclusion criteria to determine the relevance of the theme: (i) the study involved the use of medication potentially inappropriate for elderly patients; (ii) the study used a validated tool to make such an assessment.

A researcher (A.P.A.L.S.) performed an initial selection, excluding the titles that did not meet the inclusion criteria. The studies excluded were: (i) reviews and editorials, (ii) studies not written in English, Portuguese, or Spanish, (iii) studies that did not provide the full text, (iv) studies that evaluated only one or two classes of drugs, and (v) studies evaluating PIDT in only one or two diseases.

The papers that satisfied the inclusion criteria for data extraction were carefully examined regarding the following variables: country, sample size, duration, type of study, practice scenario, language of publication, limitations, and fulfillment of the items proposed by the STROBE initiative. The final analysis was performed to assess the methodological rigor of the articles published in this research area; for that purpose, the STROBE [12] tool was used. The tool’s 22 items were separated, in this study, into 34 items (Appendix I), to perform a more complete and accurate description of observational studies. In this review, each item fulfilled by the article was awarded a point, and thus the score could vary from 0 (0%) to 34 (100%) points.

RESULTS

From the various combinations of keywords, 8.610 articles were found. The first evaluation was performed by one of the evaluators (A.P.A.L.S.) who excluded 7.372 articles that did not meet at least one of the inclusion criteria. Of the remaining 1.238 articles, 484 were repeated in the databases. Thus, 754 titles were considered potentially relevant. Of these, 359 were excluded for not meeting the inclusion criteria, leaving 395 items to be evaluated according to the abstracts. In this study, 44 abstracts were not available; therefore, 351 abstracts were read and evaluated. From this evaluation, a further 144 articles were excluded for not meeting the inclusion criteria, leaving 207 articles to be read. At first, 76

articles had no free access, and 50 articles were later retrieved by the program of bibliographic commutation of the Brazilian Institute of Science and Technology (IBICT-Comut). Of the articles assessed manually, 62 did not meet the inclusion criteria. At the end of the selection process, 119 articles met the specific inclusion criteria. [13, 14, 17, 26-140] Figure 1 shows the progressive selection, the number of articles, and the reasons for exclusion at each step. The degree of agreement among the researchers was moderate for the titles ($\kappa = 0.479$) and substantial for abstracts ($\kappa_2 = 0.647$). At all stages the intervention of a third evaluator was necessary, to resolve disagreements between the two primary researchers (Figure 1).

Of the selected studies, 40.3% were performed in Europe, 32.7% in North America, and 4.2% did not indicate the country where the research was conducted. The samples observed were heterogeneous, ranging from individual patients to databases. In addition, the sample size varied from 30 patients in the study by Stuij et al. [122], to 33.830.599 prescriptions generated in the outpatients study by Lai et al.[48] and the median was 1223 patients / prescriptions.Three studies did not specify the sample size. The duration of the studies included in the review varied from one month to nine years. Notably, 79% of the studies did not indicate or specify the duration of the study.

Among the studies, 32.7% were cross-sectional and 19.3% were cohort, and 19.3% of the articles did not report which methodological design was used in the study.In addition, 22.6% did not provide a complete description of the methodological design. As for the study scenario, the most frequent were hospitals or outpatient clinics, accounting for 38.6% of the studies.In 8.4% of the studies, retirement, social security, and health plan databases were used for data collection.Only two studies were carried out in more than one study scenario [13,14]. Additionally,94.9% of the studies were written in English, and15.9% of the articles did not mention their limitations in the text.Regarding the fulfillment of the items proposed by STROBE, 49 articles met between 60% and 100% of the 34 items recommended by the initiative. (Table1)

DISCUSSION

Most of studies included were performed in the U.S.This may be related to the fact that the Beers criteria (most used/cited in the literature), the Medication Appropriateness Index (MAI), Assessing Care of Vulnerable Elders (ACOVE), Drug use review (DUR), HEDIS criteria, and Zhan criteria were developed there.The prevalence of studies and criteria developed in the U.S. ratifies the country as a pioneer in the clinical scenario, especially regarding the evaluation of pharmacotherapy [15].Additionally, several studies were conducted in Europe, which further indicates the progress of PIDT research in developed countries compared to developing countries. Therefore, it is necessary for developing countries to increase research in this area, focusing on the effectiveness of treatments and, above all, the safety of patients.

In the reviewed studies, we found a high variation in sample size, providing a comprehensive evaluation of the tools used in different sample groups.However, two studies did not clearly describe the size of the sample surveyed [16,17]. In this case, two studies indicated that the lack of information on the sample could reduce the impact of the study [12,18].Therefore, the sample in which the hypothesis is being tested should be stated and comprehensively detailed, to ensure the robustness of the study.

The largest study samples consisted of, retirement and health plan databases, for example, to evaluate PIDT.Despite being a viable strategy to assess the situational diagnosis of a sample, it is necessary to question the validity of the results obtained from databases such as these, because the use of secondary data can mask possible selection biases. According to Guaraldo et al., an active data search can decrease the over-or underestimation of drug use, because it is not known whether the patient actually used the prescribed pharmacotherapy [10].

There was a variation of 107 months between studies.Additionally, some of the manuscripts were unclear in differentiating between the time of data collection and the study duration.Thus, in most part of articles, the real time of execution of the study is not clear, which compromises the reader's understanding.According to von Elm et al., the author should describe the context in which the study is inserted, in addition to locations and relevant dates, including periods of recruitment, exposure, follow-up (if any), and data collection.Thus, an adequate description assists in the analysis of the results of the study, so that they can be incorporated into public policies and/or large interventions, if necessary. [19]

In this review, there were a large number of cross-sectional studies. The cross-sectional study can be used as an analytical study, to evaluate hypotheses of association between exposure/characteristics and event, being cost-effective, easy, and fast to perform. In addition, they describe what happens to a particular group, at a particular time, and are thus important guides for decision making in the health-planning sector [20].However, there are limitations when trying to identify the nature of the relation between exposure and event in these situations. Therefore, confounding factors must be considered in this type of study, which emphasizes the need for clinical trials to evaluate the effect of potentially inappropriate medication in the elderly population [21].Approximately 42% of the studies included in the analysis either lacked methodological rigor in the description of the study design, or did not mention it at all.Methodological rigor is necessary to provide sufficient detail, so that the reader can understand and duplicate the methodology if they wish [18].

Among the practice scenarios, there was a higher prevalence of studies performed with institutionalized elderly people, in comparison to studies with non-institutionalized elderly. Although, this prevalence exists because the criteria used for these studies have been primarily developed for evaluating the pharmacotherapy of non-institutionalized elderly patients, who have different socio-demographic and clinical characteristics from institutionalized patients [22]. Moreover, it was observed that some tools developed a priori for non-institutionalized elderly patients were used in institutions. According to Bakken et al., the application of these criteria should be carefully applied, because they can be affected by differences in study population and data source [23]. The institutionalization of patients can facilitate the collection and evaluation of data, justifying the high number of hospital-based studies [23]. In this sense, the applicability and reliability of these tools should be carefully evaluated through the analysis of the results obtained in their respective studies, to avoid reproducing the erroneous selection of criteria.

Regarding the citation of research limitations in the text, most of the studies were in agreement with Malta et al., who advocate that the manuscript should describe its limitations and consider potential sources of inaccuracy.[12] Further, the study should discuss the magnitude and direction of potential bias, which is essential for the reader's understanding, as well as evaluations by the article reviewers. [12,18]

Fewer than half of the observational articles included in the review fulfilled 60% or more of the items proposed by STROBR.Overall, the studies included in this review had no good methodological consistency. This may be related to lack of standardization of studies and the fact that the discussion of the use of PIDT be recent. The intention of the STROBE initiative is to offer a recommendation on how to report observational studies more accurately, without making recommendations or prescriptions to the design or conduction of these studies.However, adherence to the items contributes to a more accurate report of such studies, and consequently facilitates the review of these publications by editors, reviewers, and readers [12].

In general, the results of the studies included in this review indicated high levels of PIDT.Strategies to reduce the unnecessary prescription should be implemented to promote more appropriate use of these medications among this age group.The careful use of PIDT lists can assist with the detection of these drugs and prevent problems related to their use [3]. In addition to identification of PIDT, it is necessary to carry out practical interventions.A study aimed to systematically review the effects of interventions to optimize prescription found that, of the 16 studies assessed, eight reviewed the impact of educational interventions, and, of those, six showed statistically significant improvements in prescription quality. A multi-faceted approach and clearer policy guidelines are required to improve prescriptions for these vulnerable patients.[24] Moreover, strategies shown to be effective for improving prescription outcomes include educational outreach visits (academic detailing), and interventions involving a pharmacist. Pharmacist services, such as conducting medication reviews or providing advice to general practitioners, may lead to improvements in prescription outcomes.[25]

AGENDA FOR FUTURE STUDIES

Current PIDT studies are potentially valuable because, in general, their objective is to verify PIDT prevalence in various scenarios, as well as serving as a warning to health care professionals who work with elderly patients.However, more research is needed in this area, especially in developing countries, since it is necessary to evaluate the morbidity and mortality related to the use of PIDT.

To reduce the limitations of PIDT studies, an active search for data collection is needed, through which the reported prevalence of PIDT will be more reliable.Moreover, studies that relate the use of PIDT with outcomes such as adverse effects, hospitalizations, and deaths are rare, but are required to verify the real problems associated with using PIDTs.

As noted in this review, studies evaluating interventions, such as education, have shown positive results.Thus, more studies, especially randomized clinical trials, are needed to conclude whether the interventions are indeed effective.

STRENGHTS AND LIMITATIONS

Strengths were thatthis is the first review to assess the methodological rigor of studies evaluating PIDT.Obviously, our review has certain limitations. The use of English, Portuguese, and Spanish keywords can omit important publications in different languages; this limitation is common to systematic review articles. Others keys words like potential inappropriate drug therapy were not used.Furthermore, database restriction and the search strategy may have excluded important studies that

were not published in the data sources used. The exclusion criteria used in this study may have also excluded relevant studies; however, it was necessary to adopt such measures, since the review was intended to evaluate studies focusing on various diseases and medications.Moreover, no studies were analyzed that evaluated the omission or sub-use of the medication. Finally, studies that obtained negative results may not have been published.

CONCLUSION

A discussion of methodological rigor of studies evaluating PIDT is critical and can contribute to the wider discussion in health care.This review showed that PIDT is being studied mainly in developed countries, which reinforces the need for more research in developing countries.The articles included in this study focused on observing the prevalence of PIDT in various practice scenarios.Most studies were observational, and fulfilled at least 40% of the items proposed by the STROBE initiative. Our results have highlighted the potential for more detailed studies about PIDT with pratical implications to patient safety.

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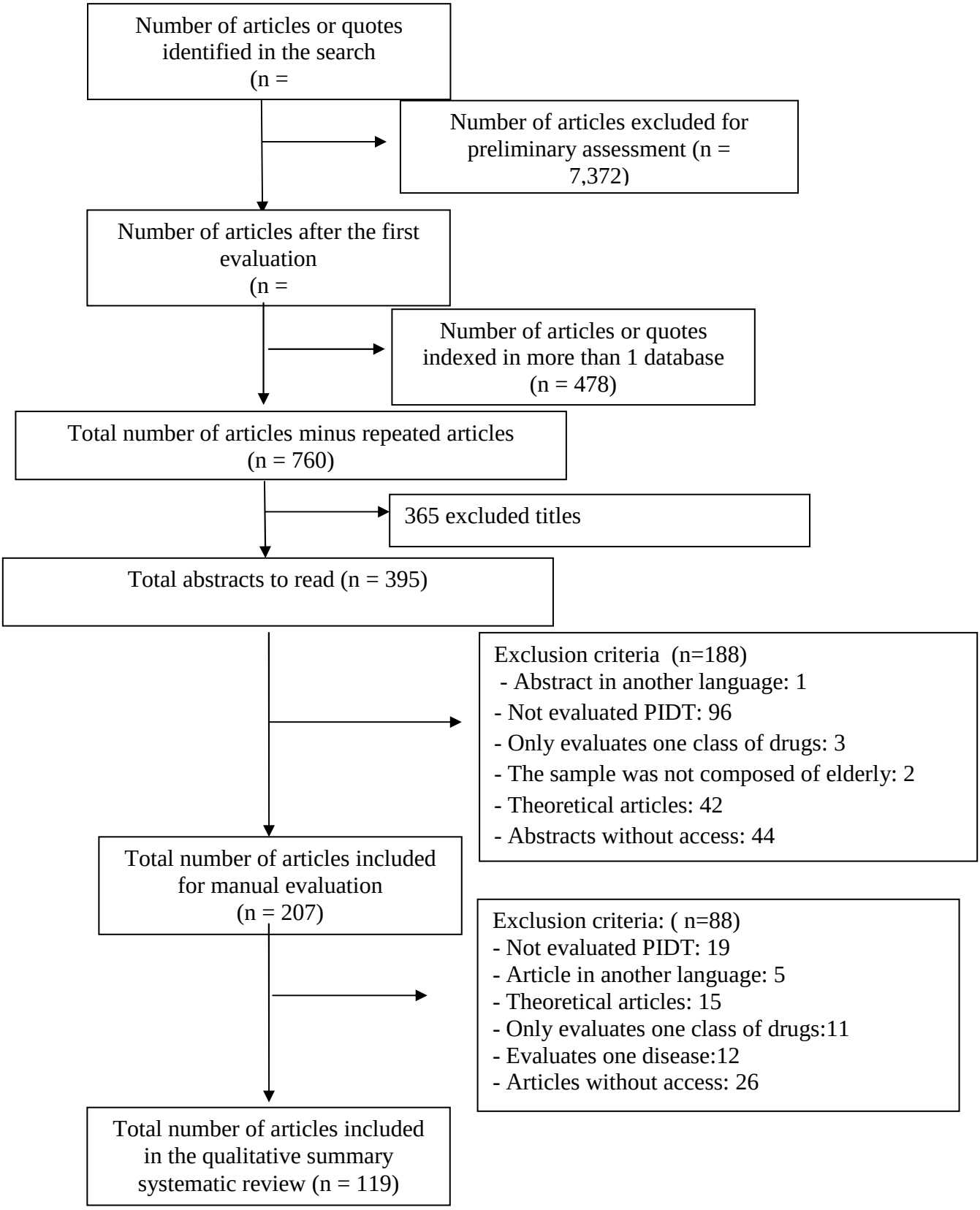
Tab1e1. Compliance of the items proposed by STROBE

Item	Percentage of articles that completed the item
(1) Indicate the study's design with a commonly used term in the title or the abstract	62,5%
(2) Provide in the abstract an informative and balanced summary of what was done and what was found	98,2%
(3) Explain the scientific background and rationale for the investigation being reported	99,1%
(4) State specific objectives, including any prespecified hypotheses	66%
(5) Present key elements of study design early in the paper	60,7%
(6) Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	90,1%
(7) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	93,7%
(8) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	0%
(9) Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	91%
(10) For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	73,2%
(11) Describe any efforts to address potential sources of bias	6,2%
(12) Explain how the study size was arrived at	27,6%
(13) Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	88,3%
(14) Describe all statistical methods, including those used to control for confounding	81,2%
(15) Describe any methods used to examine subgroups and interactions	81,2%
(16) Explain how missing data were addressed	7,1%
(17) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	76,2%

Table1. Compliance of the items proposed by STROBE (continuation)

Item	**Percentage of articles that completed the item**
(18) Describe any sensitivity analyses	26,7%
(19) Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	83%
(20) Give reasons for non-participation at each stage	83%
(21) Consider use of a flow diagram	93,7%
(22) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	88,3%
(23) Indicate the number of participants with missing data for each variable of interest	7,1%
(24) Cohort study—Summarise follow-up time (e.g., average and total amount)	13,3%
(25) Cohort study—Report numbers of outcome events or summary measures over time Case-control study—Report numbers in each exposure category, or summary measures of exposure Cross-sectional study—Report numbers of outcome events or summary measures	96,4%
(26) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	74,1%
(27) Report category boundaries when continuous variables were categorized	76,7%
(28) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	14,2%
(29) Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses.	86,6%
(30) Summarise key results with reference to study objectives.	100%
(31) Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	83%
(32) Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	97,3%
(33) Discuss the generalisability (external validity) of the study results	43.7%
(34) Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	50,8%

Figure 1. - Study selection process



CAPÍTULO 3

Comparando estudos que estimam a associação entre alguns fatores de risco e o uso da Farmacoterapia potencialmente inapropriada para o idoso: uma revisão sistemática com metanálise

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RESUMO

OBJETIVO: Comparar estudos que estimam a associação entre fatores de risco e o uso de farmacoterapia potencialmente inapropriada para o idoso. METODOLOGIA: Foi realizada uma revisão sistemática com meta-análises de estudos observacionais. As bases de dados LILACS, PubMed, Scopus e Web of Science foram revisadas. Para os estudos incluídos foram extraídos os seguintes dados: país, tipo de estudo, características da amostra, cenários de prática, instrumentos para avaliar farmacoterapia potencialmente inapropriada para o idoso e variáveis referentes aos pacientes (idade, sexo, polifarmácia). RESULTADOS: Foram incluídos 29 artigos (17 transversais, 12 coortes). A maioria dos estudos foi realizada na Europa. No que se refere à duração dos estudos, os artigos variaram de 3 a 18 meses para executarem a pesquisa. No tocante às características das amostras, todas envolviam idosos e variaram de 96 pacientes a 33.830.599 visitas ambulatoriais. Apenas a polifarmácia teve associação positiva com o uso de FPII. Todas as metanálises apresentaram elevada heterogeneidade, indicando, entre outros fatores, a falta de padronização metodológica entre os estudos incluídos.

INTRODUÇÃO

Os pacientes idosos normalmente utilizam mais medicamentos que qualquer outro grupo etário. Em média, os idosos tomam de seis a nove medicamentos em um dado momento e como representam os maiores consumidores de medicamentos, prescritos ou não prescritos, possuem maior risco para a ocorrência de eventos adversos associados a medicamentos (EAM). [1] A prevenção de EAM em idosos respresenta um ponto crucial para saúde pública dessa população vulnerável. [2] Uma das causas de EAM preveníveis é a prescrição de Farmacoterapia Potencialmente Inadequada ao Idoso (FPII). A FPII pode ser definida como a prescrição de medicamentos que pode acarretar em um risco significativo para a ocorrência de um EAM. [3,4]

Nesse sentido, diversos autores e sociedades especializadas em geriatria têm elaborado instrumentos para avaliar FPII como meio para reduzir os EAM entre idosos. [5,6] A FPII tem sido avaliada na literatura com a utilização de métodos implícitos e explícitos. Os métodos implícitos, como o Medication Reduction Project[7], são caracterizados pela revisão terapêutica específica de cada paciente, sem a padronização de um critério para a avaliação. Por outro lado, os métodos explícitos, como os critérios

de Beers, McLeod e Zhan [2,8,9], são baseados em consensos e incluem o uso de listas padronizadas contendo medicamentos que devem ser evitadas por idosos. [10]

Independente da ferramenta e do tipo, as pesquisas têm procurado apontar fatores preditivos ou que estejam associados de maneira mais próxima à FPII. Em estudo realizado por Maio et al. (2006), na Itália, os fatores associados ao uso de FPII eram a idade mais avançada, o aumento do números de medicamentos, sendo inferior para mulheres, nas regiões mais urbanas e no nível econômico superior. [11] Por outro lado, no estudo realizado por Barnett et al. (2006) a prevalência de FPII foi maior entre as mulheres estudadas em detrimento aos homens. [12] De maneira semelhante, Saab et al. (2006) apontaram como fatores preditivos para presença de FPII a presença de múltiplas morbidades, a ingestão de bebidas alcoólicas e gênero feminino. [13]

As variações encontradas também podem estar associadas ao tipo de instrumento escolhido para a avaliação. Viswanathan et al. (2005) encontraram prevalência de FPII superior com os critérios de Beers de 2003, em oposição à versão de 1997 e aos critérios de Zhan. [14] Ademais, foi admitido que a probabilidade de FPII aumentou com o número de medicamentos prescritos, mas poucos fármacos contribuem para essa elevada prevalência. Assim, como forma de ampliar as ações preventivas para reduzir os eventos adversos associados ao uso de FPII, nos sistemas de atenção à saúde de idosos é preciso realizar estudos que busquem identificar, de forma consensual, fatores preditivos para o uso desses medicamentos.

Apesar disso, a falta de padronização na realização de estudos que visam à avaliação da FPII dificulta estimar de maneira fidedigna a associação com fatores de risco . Desse modo, o objetivo desse estudo foi comparar estudos que associam entre alguns fatores de risco, como idade, sexo e polifarmácia, e o uso da Farmacoterapia potencialmente inapropriada para o idoso.

MATERIAIS E MÉTODOS

Foi realizada uma revisão sistemática com metanálises de estudos observacionais. As bases de dados LILACS, PubMed, Scopus e Web of Science foram revisadas (até Junho de 2013) para identificar estudos observacionais que avaliaram associação entre farmacoterapia potencialmente inapropriada para o idoso e fatores de risco (idade, sexo e polifarmácia). As variáveis idade, sexo e polifarmácia foram escolhidas, pois na literatura são frequentemente associadas à maior incidência de FPII.

As palavras chave utilizadas foram: “aged”, “elderly”, “inappropriate prescribing”, “drug utilization” em diferentes combinações em inglês, espanhol e português de acordo com o protocolo de busca de cada base de dados.

Nesse estudo, a polifármacia foi definida como o uso de cinco ou mais medicamentos pelo idoso. Os termos utilizados foram definidos a partir de consultas no “National Library of Medicine's controlled vocabulary thesaurus (MeSH)”. Tratam-se de conjuntos de termos em uma estrutura hierárquica que permite pesquisar em vários níveis de especificidade. Além dos termos MeSH foram utilizados outros termos não padronizados para ampliar a estratégia de busca.

Dois revisores independentes procederam com o processo de seleção dos estudos, analisando títulos, resumos e, posteriormente, artigos na íntegra, para os critérios de elegibilidade estabelecidos. Os estudos foram incluídos por consenso entre os dois revisores, com a participação de um terceiro revisor nos casos necessários.

Os estudos foram considerados elegíveis se cumpridos os seguintes critérios: (i) estudos observacionais (transversal, coorte, caso-controle) (ii) fornecimento de dados suficientes para calcular a associação entre a FPII e fatores de risco. Foram excluído (i) comentários e editoriais, (ii) estudos que não foram escritos em inglês, português e espanhol (iii) artigos que não fornecem o texto completo (iv) estudos sobre medicamentos específicos (v) estudos que não classificavam polifarmácia como o uso de cinco ou mais medicamentos (vi) estudos sobre doenças específicas.

Os estudos incluídos foram classificados em três tipos: coorte, transversal, caso-controle. Esta classificação foi realizada baseando-se no que foi determinado pelos autores dos estudos. Nos casos em que os artigos não determinaram, os autores dessa revisão os classificaram. [15,16]

Para os estudos incluídos foram extraídosos seguintes dados: país, tipo de estudo, características da amostra, cenários de prática, instrumentos para avaliar FPII e variáveis referentes aos pacientes (idade, sexo, polifarmácia).

Qualidade dos estudos

Para verificar a validade dos estudos elegíveis, a qualidade de cada relatório foi avaliado em referência à declaração STROBE [17], conforme apropriado.

Análise estatística

O desfecho primário desse estudo foi a utilização de FPII. A força da associação entre esse desfecho e o uso de mais de cinco medicamentos (polifarmácia) e o uso de

menos de quatro medicamentos foi medida por meio do risco relativo no caso de estudos de coortes e razão de prevalência no caso de estudos transversais com intervalos de confiança de 95% (IC95%). Os riscos da utilização de FPII e o peso percentual da precisão da estimativa do efeito foram estimados para cada estudo. E foram combinados usando o modelo de efeitos aleatórios por meio do teste de Mantel- Haenszel. [18]

A heterogeneidade da força da associação entre os estudos foi avaliada pelo teste Q de Cochran e pelo teste de inconsistência I^2 em que valores superiores a 50% foram considerados indicativos de elevada heterogeneidade. Uma estimativa do potencial viés de publicação foi realizada através do gráfico de funil. A simetria foi avaliada visualmente e uma distribuição assimétrica sugeriu um possível viés de publicação. Um valor de $p < 0,05$ foi considerado estatisticamente significativo. A meta-análise foi calculada usando a versão 5.0.19 Review Manager software disponível no site http://ims.cochrane.org/revman/download.[19]

RESULTADOS

Foram identificados inicialmente 11.024 artigos nas bases de dados. A Figura 1 representa o processo de seleção dos estudos de acordo com os critérios de inclusão e exclusão. Foram incluídos 29 artigos (17 transversais, 12 coortes, Zero caso-controle). [20-48]

Quanto ao país de realização dos estudos, a maioria dos estudos foi realizada nos Estados Unidos (5) e Itália (5) seguidos de Taiwan (3), Brasil (2), Índia (2), Austrália (1), Canadá (1), Espanha (1), Noruega (1), Alemanha (1), Inglaterra (1), Eslováquia (1), Turquia (1), Irã (1), Líbano (1) e Japão (1). Um dos artigos incluídos nessa revisão foi realizado em 11 países da Europa.

No que se refere à duração dos estudos, os artigos variaram de 3 a 18 meses para executarem a pesquisa. Quanto à citação da duração no texto, três não citam, 20 não deixam claro a duração.

No tocante às características das amostras, todas envolviam idosos e variaram de 96 pacientes a 33.830.599 visitas ambulatoriais. Em 19 estudos, foram incluídos idosos de 65 anos ou mais. Nos demais, foram incluídos idosos maiores ou iguais a 60 anos (3), 66 anos (2), 70 anos (2), 75 anos (1), 80 anos (1), 85 anos (1).

A maioria dos estudos coletou dados de base de dados (12) e foram realizados em hospitais (12). Quantoà língua de publicação, 27 estudos foram publicados em inglês, um em português e um em espanhol. Com relaçãoaos instrumentos para avaliar FPII, 20 estudos utilizaram os critérios de Beers nas suas diversas publicações. 24 artigos utilizaram apenas um instrumento de avaliação de FPII, enquanto que três utilizaram dois critérios e outros dois utilizaram três instrumentos distintos. Os instrumentos utilizados pelos estudos foram: critérios de Beers (20), Medication Aproppriateness Index (MAI) (1), adaptações dos critérios de Beers (3), critérios de Zhan (2), lista Francesa (1), critérios prórpios (1), STOPP (3), critérios de NORGEP (1) e os critérios de McLeod (1).

As associações avaliadas pelos estudos foram: FPII X idade (22), FPII X sexo (28), FPII X polifarmácia (9). A Tabela 1 aponta quais os estudos que avaliaram cada associação. Na metanálise em que foi realizado um modelo aleatório de nove estudos de coortes, com 2.913.127 participantes, o risco relativo de ocorrência de FPII em pacientes idosos extremos em relação aos pacientes idosos foi de 1,00. Houve heterogeneidade entre os estudos, com variabilidade muito alta (I^2 = 97%). (Figura 2).

Quanto aos estudos transversais, foram agrupados 13 estudos nessa metanálise. O resultado em que foi realizado um modelo aleatório, com 208.563.885 participantes, o risco relativo de ocorrência de FPII em pacientes idosos extremos em relação aos pacientes idosos foi de 0,98. Também houve heterogeneidade entre os estudos, com variabilidade muito alta (I^2 = 99%) (Figura 3)

No tocante a associação entre sexo e FPII, a metanálise em que foi realizado um modelo aleatório de 12 estudos de coortes, com 3.879.802 participantes, o risco relativo de ocorrência de FPII em homens extremos em relação às mulheres foi de 0,93. Houve heterogeneidade entre os estudos, com variabilidade muito alta (I^2 = 97%). (Figura 4). Quanto aos estudos transversais, foram agrupados 17 estudos nessa metanálise. O resultado em que foi realizado um modelo aleatório, com 208562524 participantes, o risco relativo de ocorrência de FPII em homens extremos em relação às mulheres foi de 0,82. Também houve heterogeneidade entre os estudos, com variabilidade muito alta (I^2 = 100%). (Figura 5)

Quatro estudos foram agrupados nessa metanálise, Onder 2003; Onder 2005; Maio 2006; Harugeri 2010, em coortes. O resultado da metanálise em que foi realizado um modelo aleatório, com 11.900 participantes, apresentou efeito estatisticamente significativo ($p < 0,001$) com um risco relativo de ocorrência de FPII em pacientes que

apresentaram polifarmácia em relação dos que não apresentaram de2,35 ($IC_{95\%}$: 1,44 a 3,83), p < 0,001. Houve heterogeneidade entre os estudos, com variabilidade muito alta (I^2 = 87%) (Figura 6).

Quanto aos estudos transversais, foram agrupados cinco estudos nessa metanálise Akaci 2005, Fialová 2005, Karandikar 2013, Nassur 2010, Nyborg 2012. O resultado da metanálise em que foi realizado um modelo aleatório, com 606.458 participantes, apresentou efeito estatisticamente significativo (p < 0,00001) com um risco relativo de ocorrência de FPII em pacientes que apresentaram polifarmácia em relação dos que não apresentaram de2,12 ($IC_{95\%}$: 1,69 a 2,65), p < 0,00001. Também houve heterogeneidade entre os estudos, com variabilidade muito alta (I^2 = 81%). (Figura 7)

DISCUSSÃO

De maneira geral, os resultados obtidos verificaram elevado grau de heterogeneidade entre os estudos incluídos, o que dificulta maiores inferências sobre a associação de alguns fatores de risco e o uso de FPII. As causas da heterogeneidade são diversas, dentre as quais, têm-se: local de realização do estudo e coleta de dados, características das amostras incluídas, diferentes instrumentos e combinações de instrumentos, entre outros. [49]

Um dos fatores que pode ter influenciado nas diferenças entre os artigos foi a realização dos estudos em países diferentes. Nessa revisão foram encontrados artigos de quatro continentes distintos. A diferença do perfil de conduta varia de país para país. Por exemplo, estudos realizados em países desenvolvidos, geralmente, contam com amostras maiores e melhor estrutura de coleta de dados, enquanto que nos países dubdesenvolvidos, as amostras são menores e apresentam maiores dificuldades para ter acesso aos dados, o que favorece a subnotificação. [50,51,52]

Outro aspecto é que a origem dos participantes dos estudos implica diferenças étnicas entre os idosos, o que podem interferir na resposta terapêutica de determinados fármacos. No caso dos eventos cardiovasculares, por exemplo, as diferenças raciais estão relacionadas a fatores genéticos que determinam a gravidade da doença e resposta a medicamentos específicos, como a isossorbida nos negros. [53,54]. Além disso, algumas RAMs estão associadas diretamente com a variabilidade genética.[55]. Portanto, as diferenças racias entre os idosos podem ser vieses relevantes que devem ser considerados ao se comparar estudos sobre FPII.

De acordo com Akazawa et al., 2010, comparações diretas entre estudos de países diferentes são difíceis, pois embora utilizem os mesmos critérios, muitas vezes estes são adaptados à realidade local. Isto ocorre devido à diversidade de incidência ou prevalência de determinadas doenças, bem como a gama de medicamentos disponíveis e utilizados pelos idosos. Vários medicamentos presentes no mercado norte-americano não são disponíveis em alguns países do Oriente Médio, por exemplo. Assim, a fim de cumprir com as suas necessidades, muitos desses países, como o Irã, desenvolveram medicamentos genéricos para aliviar suas carências. Apesar destes esforços, o número e tipos de medicamentos genéricos disponíveis são limitados. [31]

A variação do ponto de corte para idade dos idosos também pode ter contribuído para a heterogeneidade desta metanálise. A maioria dos estudos considerou idosos pacientes acima de 65 anos. Contudo, outros artigos estimaram a idade mínima de 60 anos, 70 anos, 80 anos, entre outros. [56] De acordo com a Organização Mundial de Saúde (OMS), uma pessoa é considerada idosa quando possuir 65 anos ou mais em países desenvolvidos e 60 anos ou mais em países em desenvolvimento. [57]

É importante ressaltar que esta faixa etária é larga e que diferenças de idade podem modificar a resposta ao uso medicamentos, gerando falsos resultados [58]. Por exemplo, Harugeri et al., 2010, afirmaram que os critérios de Beers são aplicáveis a pacientes com idade superior à 65 anos, mas nos países em desenvolvimento, a idade de corte para os idosos, é de 60 anos [20,21,48]. Tal fato pode influenciar no número de FPII encontrados, dificultando a comparação dos estudos analisados.

Apesar do número de FPII aumentar em idosos com mais de 80 anos, os estudos analisados divergem quanto a esta variável, o que pode influenciar na interpetação dos resultados obtidos. [21] Considerando-se que pessoas com 80 anos ou mais é o subconjunto que mais cresce no mundo, seria adequado realizar estudos que contenham apenas pacientes octagenários, reduzindo o viés da amostra.

No que se refere ao local de coleta de dados, este pode ser também uma fonte de heterogeneidade. As características de idosos hospitalizados, doenças e os medicamentos que são utilizados diferenciam das de idosos não institucionalizados. [59] Diversos estudos que avaliam FPII em todo mundo, apontam que o uso de FPII no ambiente hospitalar é mais elevado quando comparado aos demais ambientes. [60-65] Além dos estudos realizados em hospitas, houve grande participação de artigos que coletaram os dados em bases de dados.

Quanto à fonte de informação, a coleta de dados ocorrreu tanto por busca ativa em hospitais quanto em bancos de dados de serviços de saúde. Neste caso a diferença na forma de coleta pode ser mais rápida e englobar maior número de pacientes, todavia quando não há contato direto com o paciente, pode-se omitir informações, interferindo assim, nos resultados obtidos. [61]

O cenário de prática onde se avalia as FPII também pode influenciar na fidedignidade dos resultados obtidos. Por exemplo, os critérios de Beers são utilizados em diversos cenários de prática. De acordo com Page, Ruscin, 2006, esses critérios foram originalmente projetados para uso em cuidados de longa duração. Contudo, o uso dos critérios na detecção de FPII ocorre em vários cenários, incluindo farmácias e unidades de cuidados intensivos, com diferentes características tanto de cuidado prestado quanto do idoso que utiliza o serviço e dos medicamentos usados. Portanto, é necessário observar o quão aplicáveis são os critérios nos diferentes cenários, o que sugere a validação das adaptações feitas e a melhor descrição dos resultados obtidos.

Outra fonte de diferenças encontrada nessa revisão foram os diversos instrumentos utilizados para avaliar FPII. As adaptações dos critérios de Beers, por exemplo, excluem ou adicionam medicamentos não incluídos na lista original, o que dificulta a comparação entre dois estudos que os utilizam. Além disso, a comparação entre a aplicação de instrumentos explícitos e explícito-implícitos pode ser questionável, uma vez que os mesmos apresentam diferenças metodológicas. [67]

A maior diferença na aplicação entre os instrumentos explícitos e explícito-implícitos é que a experiência clínica é necessária ao utilizar o último. O MAI, por sua vez, avalia a adequação da farmacoterapia de acordo com as dez perguntas curtas que cobrem a indicação, eficácia, dose, administração, interações medicamentosas, interações fármaco-doença e custo. Os critérios de Beers, por outro lado, definem medicamento inadequado como aquele que deve ser evitado ou não utilizado em idosos, pois os riscos superam seus benefícios. [68]

Embora a literatura cite que as mulheres idosas são mais propensas que os homens a receber FPII, os distintos estudos analisados não apresentaram resultados semelhantes. Isso pode ter ocorrido por causa do processo de seleção da amostra, da incidência e prevalência de doenças mais frequentes em homens, maior população masculina no país onde o estudo foi realizado, entre outros. No entanto, os resultados obtidos nesta metanálise sugerem que não há associação entre sexo e FPII.

Apesar da elevada heterogneidade, os idosos com polifarmácia apresentaram cerca de duas vezes mais propensão à FPII. Segundo Chen et al., 2009, a relação risco/ benefício no uso de múltiplos medicamentos deve ser avaliada, pois é desfavorável em muitos idosos. Estratégias para reduzir a polifarmácia devem ser adotadas pelas equipes de saúde, a exemplo da educação em saúde com foco nos aspectos de promoção e prevenção de saúde, tanto para o idoso, como para a família e cuidadores. Além disso, a educação em saúde é importante para que o idoso possa ter autonomia e responsabilidade nas ações de autocuidado. [69,70]

Em muitos dos estudos analisados, a alta prevalência de FPII pode ser explicada em parte pela falta de conhecimento de alguns médicos sobre os riscos da prescrição de FPII, assim como por deficiências na orientação do farmacêutico que dispensam os medicamentos em hospitais ou farmácias comunitárias locais. [23] A formação de profissionais da saúde é heterogênea e estudos sugerem que vários fatores, como os problemas educacionais, socioculturais e econômicos, podem influenciar na prescrição e dispensação de medicamentos. Portanto, novos estudos devem propor intervenções que sensibilizem, motivem e eduquem profissionais de saúde no sentido de interagirem mais com os pacientes, reduzindo riscos à saúde. [33]

A principal força desse estudo é propor a primeira metanálise com estudos observacionais sobre FPII e alguns fatores de risco. Quanto as limitações, temos a elevada heterogeneidade das metanálises, o uso limitados de palavras-chave, bem como base de dados. Além disso, restrições de banco de dados e da estratégia de busca pode ter excluído estudos potenciais. Os critérios de exclusão utilizados no estudo também pode ter excluído estudos relevantes e alguns artigos são de difícil acesso. Ademais, estudos que obtiveram resultados negativos podem não ter sido publicado.

CONCLUSÃO

Os resultados obtidos mostraram elevado grau de heterogeneidade entre os estudos analisados. Novos estudos devem buscar padronizar a seleção e a estratificação da amostra e os cenários de prática, descrever minuciosamente a coleta de dados, validar os instrumentos e critérios de uso de FPII, a fim de reduzir a heterogeneidade dos estudos e facilitar a realização de revisões da literatura com metanálise pode conferir maior poder estatístico aos resultados. Somente a partir dessas medidas será possível comparar a metodologia e os resultados de estudos para gerar evidências sobre os fatores de risco e o uso de FPII.

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Figura 1. - Fluxograma com as etapas de estudo

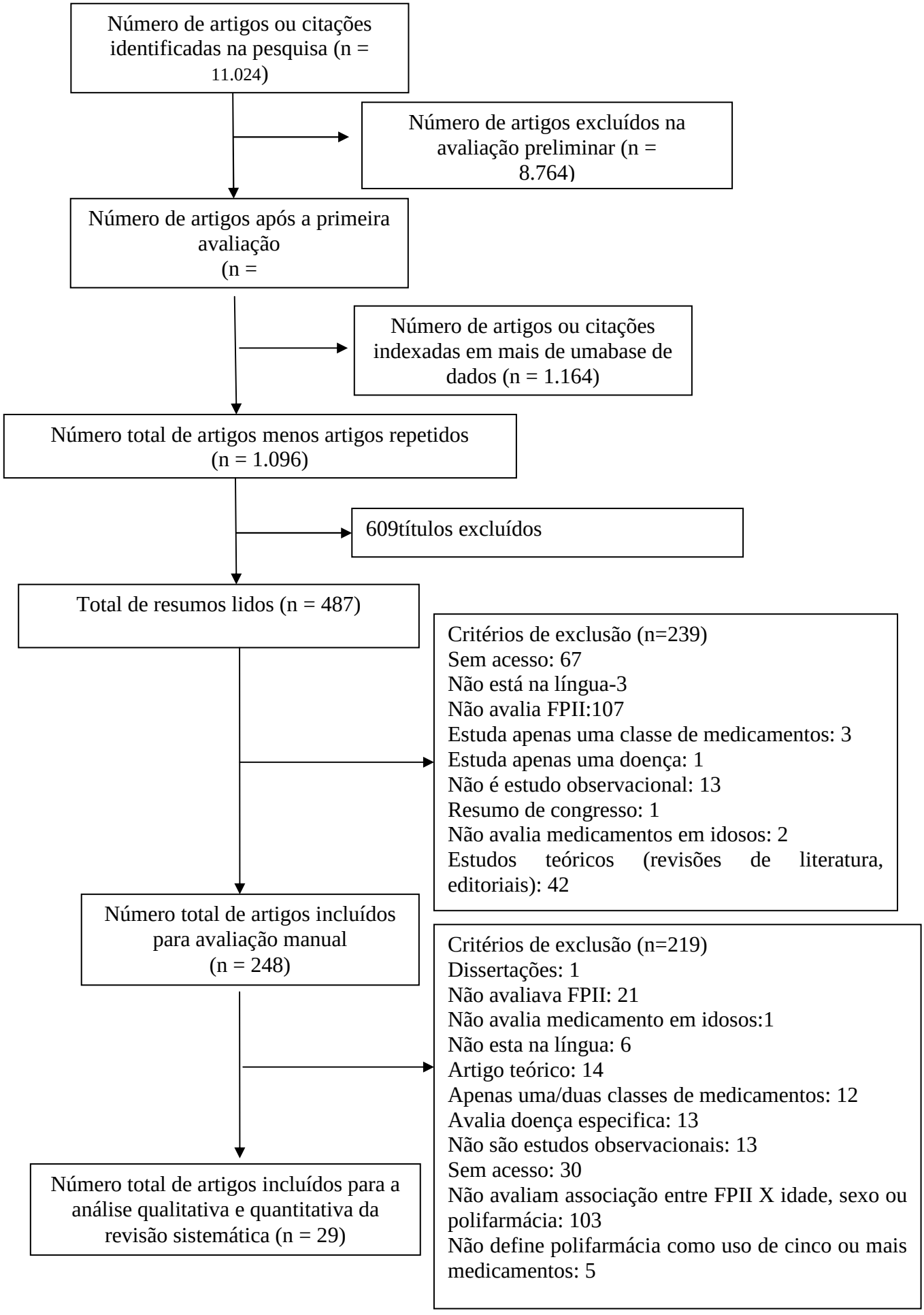


Tabela1. Características dos estudos incluídos

Estudos	Tipo de estudo	FPII X idade	FPII X sexo	FPII X polifarmácia
Akazawa, 2010	Coorte	X	X	
Bierman, 2007	Coorte		X	
Harugeri, 2010	Coorte	X	X	X
Holmes, 2013	Coorte	X	X	
Landi, 2007	Coorte		X	
Lane, 2004	Coorte	X	X	
Maio, 2006	Coorte	X	X	X
Maio, 2009	Coorte	X	X	
Onder, 2003	Coorte	X	X	X
Onder, 2005	Coorte	X	X	X
Page, 2006	Coorte	X	X	
Wawruch, 2008	Coorte		X	
Akici 2005	Transversal	X	X	X
Azoulay 2005	Transversal		X	

Figura2. Associação entre FPII e idade de acordo com o modelo aleatório - estudos de coorte.

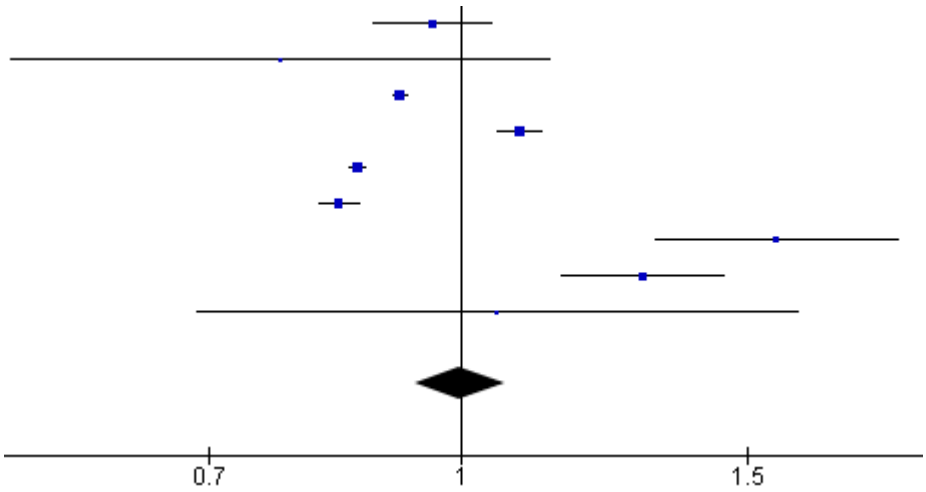


Figura3. Associação entre FPII e idade de acordo com o modelo aleatório - estudos transversais.

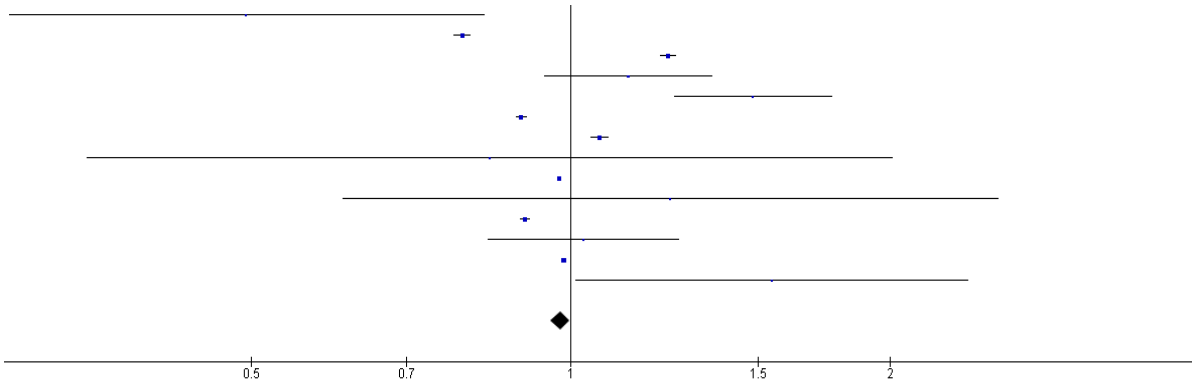


Figura 4. Associação entre FPII e sexo de acordo com o modelo aleatório - estudos de coorte.

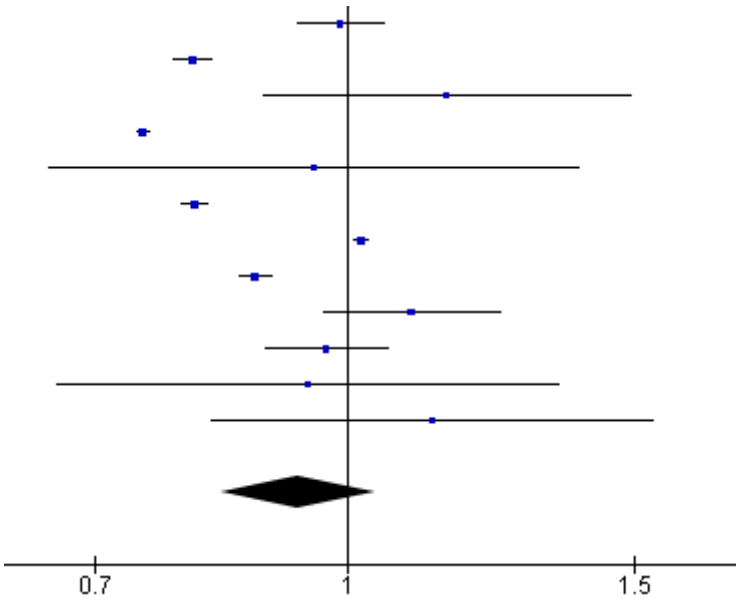


Figura 5. Associação entre FPII e sexo de acordo com o modelo aleatório - estudos transversais

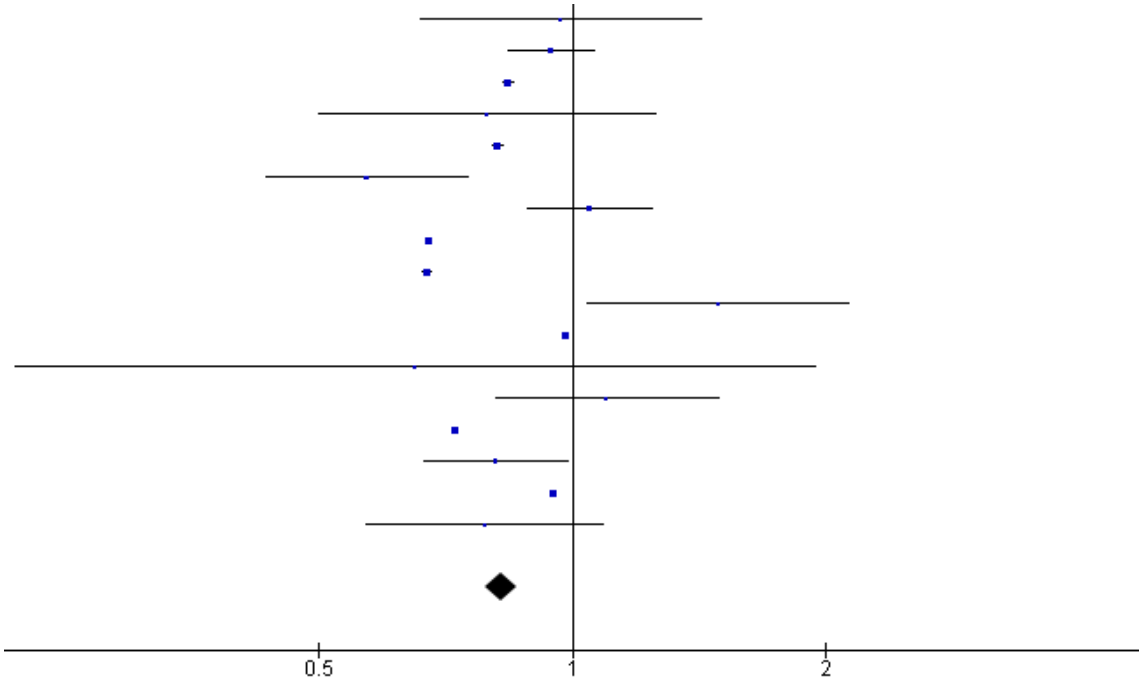


Figura6. Associação entre FPII e polifarmácia de acordo com o modelo aleatório - estudos de coorte.

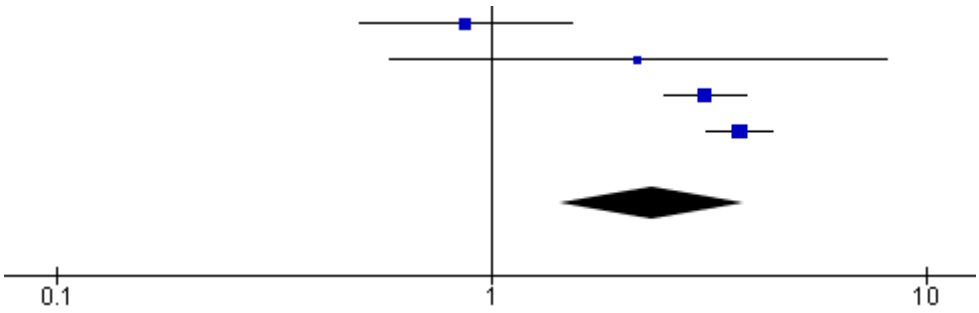
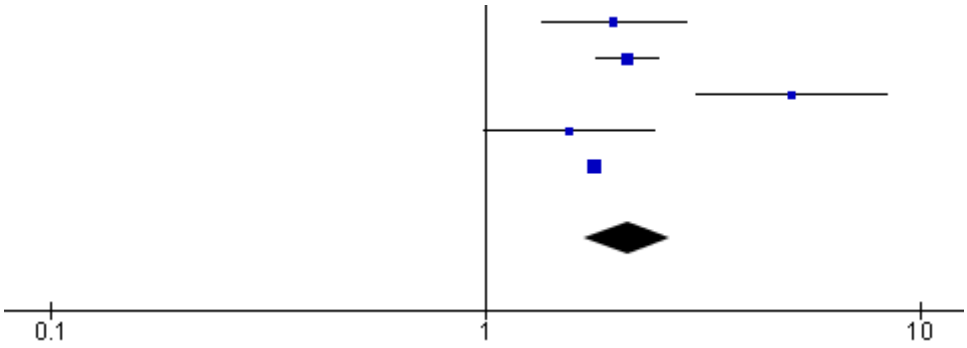


Figura 7. Associação entre FPII e polifarmácia de acordo com o modelo aleatório - estudos transversais.




CONCLUSÕES

4 CONCLUSÃO

À luz da literatura científica foi possível avaliar grande variedade de estudos sobre a FPII que apresentaram diferentes termos, instrumentos e cenários de prática. Todavia, de acordo com a iniciativa STROBE, a maioria dos estudos avaliados não demonstrou rigor metodológico, o que limita a aplicação prática de muitos desses e sua generalização. Ademais, a metanálise realizada mostrou grande heterogeneidade dos estudos, sendo necessário investir na melhor padronização das amostras, na descrição das metodologias, validação de critérios e de instrumentos. O conjunto dos resultados obtidos sugere que estudos sobre FPII são necessários e ainda precisam ser melhor executados, a fim de proporcionar maior segurança ao idosos que precisam usar medicamentos.

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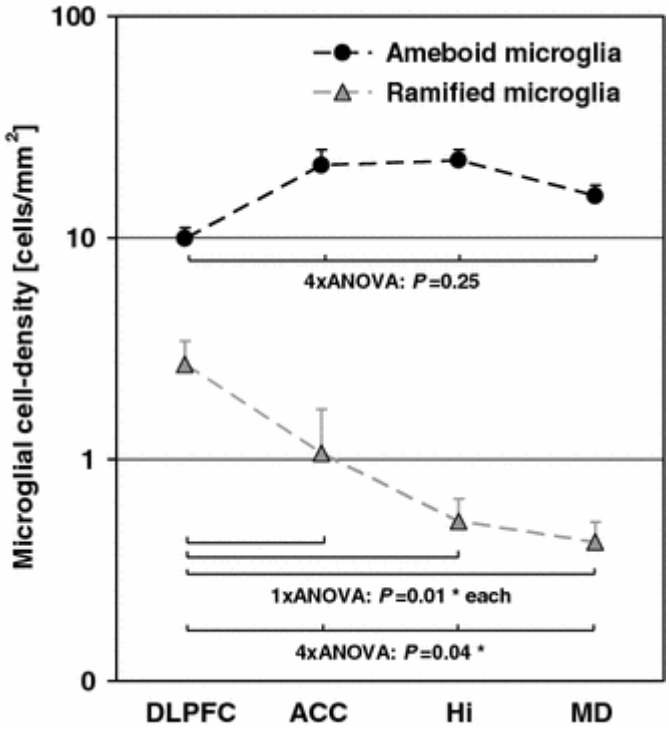

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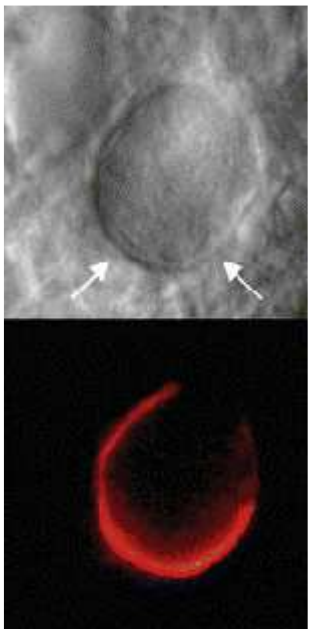

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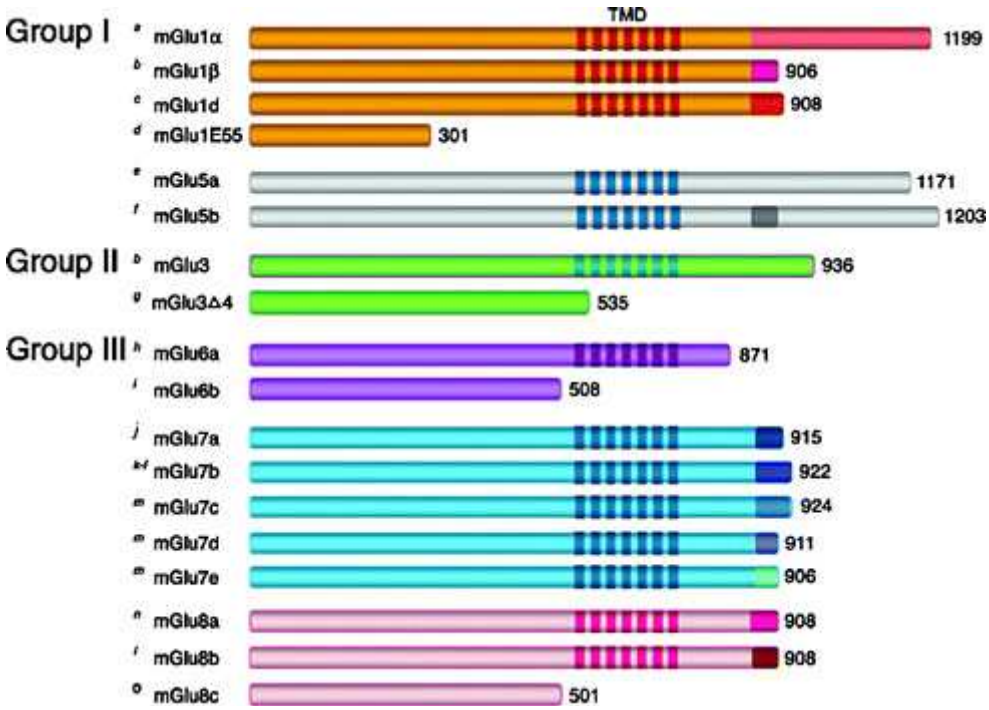

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Your cover letter should not include requests to reduce or waive publication fees. Should your manuscript be accepted, you will have the opportunity to include your requests at that time. See *PLOS ONE* Editorial Policy for more information regarding publication fees.

Manuscript Organization

PLOS ONE considers manuscripts of any length. There are no explicit restrictions for the number of words, figures, or the length of the supporting information, although we encourage a concise and accessible writing style. We will not consider monographs.

All manuscripts should be double-spaced and include line numbers and page numbers.

Manuscripts should begin with the ordered sections:

- Title
- Authors
- Affiliations
- Abstract
- Introduction

and end with the sections of:

- Acknowledgments
- References
- Figure Legends
- Tables

Figures should not be included in the main manuscript file. Each figure must be prepared and submitted as an individual file. Find more information about preparing figures here.

The title, authors, and affiliations should all be included on a title page as the first page of the manuscript file.

There are no explicit requirements for section organization between these beginning and ending sections. Articles may be organized in different ways and with different section titles, according to the authors' preference. In most cases, internal sections include:

- Materials and Methods
- Results
- Discussion
- Conclusions (optional)

PLOS ONE has no specific requirements for the order of these sections, and in some cases it may be appropriate to combine sections. Guidelines for individual sections can be found below.

Abbreviations should be kept to a minimum and defined upon first use in the text. Non-standard abbreviations should not be used unless they appear at least three times in the text.

Standardized nomenclature should be used as appropriate, including appropriate usage of species names and SI units.

Manuscript File Type Requirements

Authors may submit their manuscript files in Word (as .doc or .docx), LaTeX (as .pdf), or RTF format. Only RTF and .doc files can be used during the production process. Word files must not be protected.

LaTeX Submissions. If you would like to submit your manuscript using LaTeX, you must author your article using the *PLOS ONE* LaTeX template and BibTeX style sheet. Articles prepared in LaTeX may be submitted in PDF format for use during the review process. After acceptance, however, .tex files and formatting information will be required as a zipped file. Please consult our LaTeX guidelines for a list of what will be required.

Submissions with equations. If your manuscript is or will be in .docx format and contains equations, you must follow the instructions below to make sure that your equations are editable when the file enters production.

If you have not yet composed your article, you can ensure that the equations in your .docx file remain editable in .doc by enabling "Compatibility Mode" before you begin. To do this, open a new document and save as Word 97-2003 (*.doc). Several features of Word 2007/10 will now be inactive, including the built-in equation editing tool. You can insert equations in one of the two ways listed below.

If you have already composed your article as .docx and used its built-in equation editing tool, your equations will become images when the file is saved down to .doc. To resolve this problem, re-key your equations in one of the two following ways.

1. Use MathType to create the equation (recommended)
2. Go to Insert > Object > Microsoft Equation 3.0 and create the equation

If, when saving your final document, you see a message saying "Equations will be converted to images," your equations are no longer editable and PLoS will not be able to accept your file.

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2. Guidelines for Standard Sections

Title

Manuscripts must be submitted with both a full title and a short title, which will appear at the top of the PDF upon publication if accepted. Only the full title should be included in the manuscript file; the short title will be entered during the online submission process.

The full title must be 250 characters or fewer. It should be specific, descriptive, concise, and comprehensible to readers outside the subject field. Avoid abbreviations if possible. Where appropriate, authors should include the species or model system used (for biological papers) or type of study design (for clinical papers).

Examples:

- Impact of Cigarette Smoke Exposure on Innate Immunity: A *Caenorhabditis elegans* Model
- Solar Drinking Water Disinfection (SODIS) to Reduce Childhood Diarrhoea in Rural Bolivia: A Cluster-Randomized, Controlled Trial

The short title must be 50 characters or fewer and should state the topic of the paper.

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Authors and Affiliations

All author names should be listed in the following order:

- First names (or initials, if used),
- Middle names (or initials, if used), and
- Last names (surname, family name)

Each author should list an associated department, university, or organizational affiliation and its location, including city, state/province (if applicable), and country. If the article has been submitted on behalf of a consortium, all author names and affiliations should be listed at the end of the article.

This information cannot be changed after initial submission, so please ensure that it is correct.

To qualify for authorship, a researcher should contribute to all of the following:

1. Conception and design of the work, acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content
3. Final approval of the version to be published

All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Those who contributed to the work but do not qualify for authorship should be listed in the acknowledgments.

When a large group or center has conducted the work, the author list should include the individuals whose contributions meet the criteria defined above, as well as the group name.

One author should be designated as the corresponding author, and his or her email address or other contact information should be included on the manuscript cover page. This information will be published with the article if accepted.

See the *PLOS ONE* Editorial Policy regarding authorship criteria for more information.

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Abstract

The abstract should:

- Describe the main objective(s) of the study
- Explain how the study was done, including any model organisms used, without methodological detail

- Summarize the most important results and their significance
- Not exceed 300 words

Abstracts should not include:

- Citations
- Abbreviations, if possible

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Introduction

The introduction should:

- Provide background that puts the manuscript into context and allows readers outside the field to understand the purpose and significance of the study
- Define the problem addressed and why it is important
- Include a brief review of the key literature
- Note any relevant controversies or disagreements in the field
- Conclude with a brief statement of the overall aim of the work and a comment about whether that aim was achieved

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Materials and Methods

This section should provide enough detail to allow suitably skilled investigators to fully replicate your study. Specific information and/or protocols for new methods should be included in detail. If materials, methods, and protocols are well established, authors may cite articles where those protocols are described in detail, but the submission should include sufficient information to be understood independent of these references.

We encourage authors to submit detailed protocols for newer or less well-established methods as Supporting Information. Further information about formatting Supporting Information files, can be found here.

Methods sections of papers on research using human or animal subjects and/or tissue or field sampling must include required ethics statements. See theReporting Guidelines for human research, clinical trials, animal research, and observational and field studies for more information.

Methods sections of papers with data that should be deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers and version numbers, if appropriate. Accession numbers should be provided in parentheses after the entity on first use. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication. A list of recommended repositories for different types of data can be found here.

Methods sections of papers using cell lines must state the origin of the cell lines used. See the Reporting Guidelines for cell line research for more information.

Methods sections of papers adding new taxon names to the literature must follow the Reporting Guidelines below for a new zoological taxon, botanical taxon, or fungal taxon.

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Results, Discussion, and Conclusions

These sections may all be separate, or may be combined to create a mixed Results/Discussion section (commonly labeled "Results and Discussion") or a mixed Discussion/Conclusions section (commonly labeled "Discussion"). These sections may be further divided into subsections, each with a concise subheading, as appropriate. These sections have no word limit, but the language should be clear and concise.

Together, these sections should describe the results of the experiments, the interpretation of these results, and the conclusions that can be drawn. Authors should explain how the results relate to the hypothesis presented as the basis of the study and provide a succinct explanation of the implications of the findings, particularly in relation to previous related studies and potential future directions for research.

PLOS ONE editorial decisions do not rely on perceived significance or impact, so authors should avoid overstating their conclusions. See the *PLOS ONE* Publication Criteria for more information.

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Acknowledgments

People who contributed to the work but do not fit the *PLOS ONE* authorship criteria should be listed in the acknowledgments, along with their contributions. You must ensure that anyone named in the acknowledgments agrees to being so named.

Funding sources should not be included in the acknowledgments, or anywhere in the manuscript file. You will provide this information during the manuscript submission process.

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References

Only published or accepted manuscripts should be included in the reference list. Manuscripts that have been submitted but not yet accepted should not be cited. Limited citation of unpublished work should be included in the body of the text only as "unpublished data."

References must be listed at the end of the manuscript and numbered in the order that they appear in the text. In the text, citations should be indicated by the reference number in brackets. Journal name abbreviations should be those found in the NCBI databases. A number of reference software companies supply PLOS style files (e.g., Reference Manager, EndNote).

References should be formatted as follows:

- Published papers. Hou WR, Hou YL, Wu GF, Song Y, Su XL, et al. (2011) cDNA, genomic sequence cloning and overexpression of ribosomal protein gene L9 (rpL9) of the giant panda (*Ailuropoda melanoleuca*). Genet Mol Res 10: 1576-1588. Note: Use of a DOI number for the full-text article is acceptable as an alternative to or in addition to traditional volume and page numbers.

- Accepted, unpublished papers. Same as above, but "In press" appears instead of the page numbers.

- Electronic journal articles. Huynen MMTE, Martens P, Hilderlink HBM (2005) The health impacts of globalisation: a conceptual framework. Global Health 1: 14.

Available: http://www.globalizationandhealth.com/content/1/1/14. Accessed 25 January 2012.

- Books. Bates B (1992) Bargaining for life: A social history of tuberculosis. Philadelphia: University of Pennsylvania Press. 435 p.

- Book chapters Hansen B (1991) New York City epidemics and history for the public. In: Harden VA, Risse GB, editors. AIDS and the historian. Bethesda: National Institutes of Health. pp. 21-28.

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Tables

Tables should be included at the end of the manuscript. All tables should have a concise title. Footnotes can be used to explain abbreviations. Citations should be indicated using the same style as outlined above. Tables occupying more than one printed page should be avoided, if possible. Larger tables can be published as Supporting Information. Please ensure that table formatting conforms to our Guidelines for table preparation.

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Figure Legends

Figures should not be included in the manuscript file, but figure legends should be. Guidelines for preparing figures can be found here.

Figure legends should describe the key messages of a figure. Legends should have a short title of 15 words or less. The full legend should have a description of the figure and allow readers to understand the figure without referring to the text. The legend itself should be succinct, avoid lengthy descriptions of methods, and define all non-standard symbols and abbreviations.

Further information about figure legends can be found in the Figure Guidelines.

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Striking Images

Authors are encouraged to upload a "striking image" that may be used to represent their paper online in places like the journal homepage or in search results. The striking image must be derived from a figure or supporting information file from the paper, ie. a cropped portion of an image or the entire image. Striking images should ideally be high resolution, eye-catching, single panel images, and should ideally avoid containing added details such as text, scale bars, and arrows. If no striking image is uploaded, a figure from the paper will be designated as the striking image.

Please keep in mind that PLOS's Creative Commons Attribution License applies to striking images. As such, do not submit any figures or photos that have been previously copyrighted unless you have express written permission from the copyright holder to publish under the CCAL license. Note that all published materials in PLOS ONE are freely available online, and any third party is permitted to read, download, copy, distribute, and use these materials in any way, even commercially, with proper attribution.

Care should be taken with the following image types in particular:

1. PLOS ONE is unable to publish any images generated by Google software (Google Maps, Street View, and Earth)
2. Maps in general are usually copyrighted, especially satellite maps
3. Photographs
4. Commercial or government images, slogans, or logos
5. Images from Facebook or Twitter

Authors must also take special care when submitting manuscripts that contain potentially identifying images of people. Identifying information should not be included in the manuscript unless the information is crucial and the individual has provided written consent by completing the Consent Form for Publication in a PLOS Journal (PDF).

For license inquiries, e-mail license [at] plos.org.

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3. Specific Reporting Guidelines

Human Subject Research

Methods sections of papers on research using human subject or samples must include ethics statements that specify:

- The name of the approving institutional review board or equivalent committee(s). If approval was not obtained, the authors must provide a detailed statement explaining why it was not needed
- Whether informed consent was written or oral. If informed consent was oral, it must be stated in the manuscript:
  - Why written consent could not be obtained
  - That the Institutional Review Board (IRB) approved use of oral consent
  - How oral consent was documented

For studies involving humans categorized by race/ethnicity, age, disease/disabilities, religion, sex/gender, sexual orientation, or other socially constructed groupings, authors should:

- Explicitly describe their methods of categorizing human populations
- Define categories in as much detail as the study protocol allows
- Justify their choices of definitions and categories, including for example whether any rules of human categorization were required by their funding agency
- Explain whether (and if so, how) they controlled for confounding variables such as socioeconomic status, nutrition, environmental exposures, or similar factors in their analysis

In addition, outmoded terms and potentially stigmatizing labels should be changed to more current, acceptable terminology. Examples: "Caucasian" should be changed to "white" or "of [Western] European descent" (as appropriate); "cancer victims" should be changed to "patients with cancer."

For papers that include identifying, or potentially identifying, information, authors must download the Consent Form for Publication in a PLOS Journal (PDF), which the individual, parent, or guardian must sign once they have read the paper and been informed about the terms of PLOS open-access license. The signed consent form should not be submitted with the manuscript, but authors should securely file it in the

individual's case notes and the methods section of the manuscript should explicitly state that consent authorization for publication is on file, using wording like:

The individual in this manuscript has given written informed consent (as outlined in PLOS consent form) to publish these case details.

For more information about *PLOS ONE* policies regarding human subject research, see the Publication Criteria and Editorial Policies.

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Clinical Trials

Authors of manuscripts describing the results of clinical trials must adhere to the CONSORT reporting guidelines appropriate to their trial design, available on the CONSORT Statement website. Before the paper can enter peer review, authors must:

1. Provide the registry name and number in the methods section of the manuscript
2. Provide a copy of the trial protocol as approved by the ethics committee and a completed CONSORT checklist as Supporting Information (which will be published alongside the paper, if accepted)
3. Include the CONSORT flow diagram as the manuscript's "Figure 1"

Any deviation from the trial protocol must be explained in the paper. Authors must explicitly discuss informed consent in their paper, and we reserve the right to ask for a copy of the patient consent form.

The methods section must include the name of the registry, the registry number, and the URL of your trial in the registry database for each location in which the trial is registered.

For more information about *PLOS ONE* policies regarding clinical trials, see the Editorial Policies.

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Animal Research

Methods sections of manuscripts reporting results of animal research must include required ethics statements that specify:

- The full name of the relevant ethics committee that approved the work, and the associated permit number(s) (where ethical approval is not required, the manuscript should include a clear statement of this and the reason why)
- Relevant details for efforts taken to ameliorate animal suffering

For example:

This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The protocol was approved by the Committee on the Ethics of Animal Experiments of the University of Minnesota (Permit Number: 27-2956). All surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering.

The organism(s) studied should always be stated in the abstract. Where research may be confused as pertaining to clinical research, the animal model should also be stated in the title.

We ask authors to follow the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines for all submissions describing laboratory-based animal research and to upload a completed ARRIVE Guidelines Checklist to be published as supporting information. Please note that inclusion of a completed ARRIVE Checklist will be a formal requirement for publication at a later date.

For more information about *PLOS ONE* policies regarding animal research, see the Publication Criteria and Editorial Policies.

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Observational and Field Studies

Methods sections for submissions reporting on any type of field study must include ethics statements that specify:

- Permits and approvals obtained for the work, including the full name of the authority that approved the study; if none were required, authors should explain why
- Whether the land accessed is privately owned or protected

- Whether any protected species were sampled
- Full details of animal husbandry, experimentation, and care/welfare, where relevant

For more information about *PLOS ONE* policies regarding observational and field studies, see the Publication Criteria and Editorial Policies.

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Cell Line Research

Methods sections for submissions reporting on research with cell lines should state the origin of any cell lines. For established cell lines the provenance should be stated and references must also be given to either a published paper or to a commercial source. If previously unpublished *de novo* cell lines were used, including those gifted from another laboratory, details of institutional review board or ethics committee approval must be given, and confirmation of written informed consent must be provided if the line is of human origin.

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Systematic Review/Meta-Analysis

A systematic review paper, as defined by The Cochrane Collaboration, is a review of a clearly formulated question that uses explicit, systematic methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. These reviews differ substantially from narrative-based reviews or synthesis articles. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies.

Reports of systematic reviews and meta-analyses must include a completed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist and flow diagram to accompany the main text. Blank templates are available here:

- Checklist: PDF or Word document
- Flow diagram: PDF or Word document

Authors must also state in their "Methods" section whether a protocol exists for their systematic review, and if so, provide a copy of the protocol as Supporting Information and provide the registry number in the abstract.

If your article is a Systematic Review or a Meta-Analysis you should:

- State this in your cover letter
- Select "Research Article" as your article type when submitting
- Include the PRISMA flowchart as Figure 1 (required where applicable)
- Include the PRISMA checklist as Supporting Information

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Paleontology and Archaeology Research

Manuscripts reporting paleontology and archaeology research must include descriptions of methods and specimens in sufficient detail to allow the work to be reproduced. Data sets supporting statistical and phylogenetic analyses should be provided, preferably in a format that allows easy re-use.

Specimen numbers and complete repository information, including museum name and geographic location, are required for publication. Locality information should be provided in the manuscript as legally allowable, or a statement should be included giving details of the availability of such information to qualified researchers.

If permits were required for any aspect of the work, details should be given of all permits that were obtained, including the full name of the issuing authority. This should be accompanied by the following statement:

All necessary permits were obtained for the described study, which complied with all relevant regulations.

If no permits were required, please include the following statement:

No permits were required for the described study, which complied with all relevant regulations.

See the *PLOS ONE* Editorial Policies for more information regarding manuscripts describing paleontology and archaeology research.

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Software Papers

Manuscripts describing software should provide full details of the algorithms designed. Describe any dependencies on commercial products or operating system. Include details of the supplied test data and explain how to install and run the software. A brief description of enhancements made in the major releases of the software may also be given. Authors should provide a direct link to the deposited software from within the paper.

See the *PLOS ONE* Editorial Policies for more information about submitting manuscripts.

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Database Papers

For descriptions of databases, provide details about how the data were curated, as well as plans for long-term database maintenance, growth, and stability. Authors should provide a direct link to the database hosting site from within the paper.

See the *PLOS ONE* Editorial Policies for more information about submitting manuscripts describing databases.

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New Zoological Taxon

For proper registration of a new zoological taxon, we require two specific statements to be included in your manuscript.

In the Results section, the globally unique identifier (GUID), currently in the form of a Life Science Identifier (LSID), should be listed under the new species name, for example:

Anochetus boltoni Fisher sp. nov. urn:lsid:zoobank.org:act:B6C072CF-1CA6-40C7-8396-534E91EF7FBB

You will need to contact Zoobank to obtain a GUID (LSID). Please do this as early as possible to avoid delay of publication upon acceptance of your manuscript. It is your responsibility to provide us with this information so we can include it in the final published paper.

Please also insert the following text into the Methods section, in a sub-section to be called "Nomenclatural Acts":

The electronic edition of this article conforms to the requirements of the amended International Code of Zoological Nomenclature, and hence the new names contained herein are available under that Code from the electronic edition of this article. This published work and the nomenclatural acts it contains have been registered in ZooBank, the online registration system for the ICZN. The ZooBank LSIDs (Life Science Identifiers) can be resolved and the associated information viewed through any standard web browser by appending the LSID to the prefix "http://zoobank.org/". The LSID for this publication is: urn:lsid:zoobank.org:pub: XXXXXXX. The electronic edition of this work was published in a journal with an ISSN, and has been archived and is available from the following digital repositories: PubMed Central, LOCKSS [author to insert any additional repositories].

All *PLOS ONE* articles are deposited in PubMed Central and LOCKSS. If your institute, or those of your co-authors, has its own repository, we recommend that you also deposit the published online article there and include the name in your article.

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New Botanical Taxon

When publishing papers that describe a new botanical taxon, PLOS aims to comply with the requirements of the International Code of Nomenclature for algae, fungi, and plants (ICN). In association with the International Plant Names Index (IPNI), the following guidelines for publication in an online-only journal have been agreed such that any scientific botanical name published by us is considered effectively published under the rules of the Code. Please note that these guidelines differ from those for zoological nomenclature, and apply only to seed plants, ferns, and lycophytes.

Effective January 2012, "the description or diagnosis required for valid publication of the name of a new taxon" can be in either Latin or English. This does not affect the requirements for scientific names, which are still to be Latin.

Also effective January 2012, the electronic PDF represents a published work according to the ICN for algae, fungi, and plants. Therefore the new names contained in the

electronic publication of a *PLOS ONE* article are effectively published under that Code from the electronic edition alone, so there is no longer any need to provide printed copies.

Additional information describing recent changes to the Code can be found here.

For proper registration of the new taxon, we require two specific statements to be included in your manuscript.

In the Results section, the globally unique identifier (GUID), currently in the form of a Life Science Identifier (LSID), should be listed under the new species name, for example:

> Solanum aspersum S.Knapp, sp. nov. [urn:lsid:ipni.org:names:77103633-1] Type: Colombia. Putumayo: vertiente oriental de la Cordillera, entre Sachamates y San Francisco de Sibundoy, 1600-1750 m, 30 Dec 1940, J. Cuatrecasas 11471 (holotype, COL; isotypes, F [F-1335119], US [US-1799731]).

PLOS ONE staff will contact IPNI to obtain the GUID (LSID) after your manuscript is accepted for publication, and this information will then be added to the manuscript during the production phase

In the Methods section, include a sub-section called "Nomenclature" using the following wording:

The electronic version of this article in Portable Document Format (PDF) in a work with an ISSN or ISBN will represent a published work according to the International Code of Nomenclature for algae, fungi, and plants, and hence the new names contained in the electronic publication of a PLOS ONE article are effectively published under that Code from the electronic edition alone, so there is no longer any need to provide printed copies.
In addition, new names contained in this work have been submitted to IPNI, from where they will be made available to the Global Names Index. The IPNI LSIDs can be resolved and the associated information viewed through any standard web browser by appending the LSID contained in this publication to the prefix http://ipni.org/. The online version of this work is archived and available from the following digital

repositories: [INSERT NAMES OF DIGITAL REPOSITORIES WHERE ACCEPTED MANUSCRIPT WILL BE SUBMITTED (PubMed Central, LOCKSS etc)].

All *PLOS ONE* articles are deposited in PubMed Central and LOCKSS. If your institute, or those of your co-authors, has its own repository, we recommend that you also deposit the published online article there and include the name in your article.

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New Fungal Taxon

When publishing papers that describe a new fungal taxon name, PLOS aims to comply with the requirements of the International Code of Nomenclature for algae, fungi, and plants (ICN). The following guidelines for publication in an online-only journal have been agreed such that any scientific fungal name published by us is considered effectively published under the rules of the Code. Please note that these guidelines differ from those for zoological nomenclature.

Effective January 2012, "the description or diagnosis required for valid publication of the name of a new taxon" can be in either Latin or English. This does not affect the requirements for scientific names, which are still to be Latin.

Also effective January 2012, the electronic PDF represents a published work according to the ICN for algae, fungi, and plants. Therefore the new names contained in the electronic publication of a *PLOS ONE* article are effectively published under that Code from the electronic edition alone, so there is no longer any need to provide printed copies.

Additional information describing recent changes to the Code can be found here.

For proper registration of the new taxon, we require two specific statements to be included in your manuscript.

In the Results section, the globally unique identifier (GUID), currently in the form of a Life Science Identifier (LSID), should be listed under the new species name, for example:

Hymenogaster huthii. Stielow et al. 2010, sp. nov. [urn:lsid:indexfungorum.org:names:518624]

You will need to contact either Mycobank or Index Fungorum to obtain the GUID (LSID). Please do this as early as possible to avoid delay of publication upon acceptance of your manuscript. It is your responsibility to provide us with this information so we can include it in the final published paper. Effective January 2013, all papers describing new fungal species must reference the identifier issued by a recognized repository in the protologue in order to be considered effectively published.

In the Methods section, include a sub-section called "Nomenclature" using the following wording (this example is for taxon names submitted to MycoBank; please substitute appropriately if you have submitted to Index Fungorum):

The electronic version of this article in Portable Document Format (PDF) in a work with an ISSN or ISBN will represent a published work according to the International Code of Nomenclature for algae, fungi, and plants, and hence the new names contained in the electronic publication of a PLOS ONE article are effectively published under that Code from the electronic edition alone, so there is no longer any need to provide printed copies.
In addition, new names contained in this work have been submitted to MycoBank from where they will be made available to the Global Names Index. The unique MycoBank number can be resolved and the associated information viewed through any standard web browser by appending the MycoBank number contained in this publication to the prefix http://www.mycobank.org/MB/. The online version of this work is archived and available from the following digital repositories: [INSERT NAMES OF DIGITAL REPOSITORIES WHERE ACCEPTED MANUSCRIPT WILL BE SUBMITTED (PubMed Central, LOCKSS etc)].

All *PLOS ONE* articles are deposited in PubMed Central and LOCKSS. If your institute, or those of your co-authors, has its own repository, we recommend that you also deposit the published online article there and include the name in your article.

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Qualitative Research

Qualitative research studies use non-quantitative methods to address a defined research question that may not be accessible by quantitative methods, such as people's interpretations, experiences, and perspectives. The analysis methods are explicit,

systematic, and reproducible, but the results do not involve numerical values or use statistics. Examples of qualitative data sources include, but are not limited to, interviews, text documents, audio/video recordings, and free-form answers to questionnaires and surveys.

Qualitative research studies should be reported in accordance to the Consolidated criteria for reporting qualitative research (COREQ) checklist. Further reporting guidelines can be found in the Equator Network's Guidelines for reporting qualitative research.