**UNIVERSIDADE FEDERAL DE ALFENAS**

**DANIELLE APARECIDA FERREIRA DE OLIVEIRA MARRAFON**

# avaliação das reações adversas dos analgésicos tapentadol, viminol e dipirona em um contexto de saúde baseado em evidência

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**DANIELLE APARECIDA FERREIRA DE OLIVEIRA MARRAFON**

# AVALIAÇÃO DAS REAÇÕES ADVERSAS DOS ANALGÉSICOS TAPENTADOL, VIMINOL E DIPIRONA EM UM CONTEXTO DE SAÚDE BASEADO EM EVIDÊNCIA

Tese apresentada como parte dos requisitos para obtenção do título de Doutor em Ciências Farmacêuticas pela Universidade Federal de Alfenas. Área de concentração: Bioquímica e Farmacologia Aplicada às Ciências Farmacêuticas

Orientadora: Prof. Drª Larissa Helena Lobo Torres Pacheco
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O(A) Presidente da banca examinadora abaixo assina a aprovação a Tese apresentada como parte dos requisitos para a obtenção do título de Doutor em Ciências Farmacêuticas pela Universidade Federal de Alfenas. Área de concentração: Ciências Farmacêuticas

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*“Pedras no caminho? Eu guardo todas, um dia vou construir um castelo....”*

(Nemo Nox, 2003)

## RESUMO

Os analgésicos são amplamente utilizados, porém a segurança da dipirona, viminol e tapentadol permanece pouco compreendida. Os objetivos deste estudo foram transmitir o conhecimento em farmacovigilância (FV) para a implantação de um serviço hospitalar; avaliar as reações adversas a medicamentos (RAM) no uso dos três analgésicos em uma Clínica da Dor e revisar sistematicamente a segurança e eficácia do viminol. Na **etapa A**, o objetivo foi avaliar o impacto do treinamento em FV nos profissionais hospitalares. Antes e após o treinamento, o participante respondeu a um questionário, sendo contabilizada a aquisição de conhecimento em comparação às respostas do padrão ouro. Participaram da pesquisa 129 profissionais. Antes do treinamento, todos apresentaram algum conhecimento sobre FV, 7%, uma compreensão mediana, 93% revelaram compreensão insatisfatória e nenhum participante, compreensão satisfatória e total. Após treinamento, 56,6%; 30,2%; 12,4% e 0,8% dos participantes apresentaram compreensão mediana, insatisfatória, satisfatória e total, respectivamente. O treinamento foi eficaz com aumento de notificações espontâneas. Na **etapa B**, avaliaram-se prospectivamente as RAM dos três analgésicos na Clínica da Dor da Santa Casa de Alfenas. Os pacientes foram acompanhados por até 45 dias, as RAM foram notificadas e classificadas de acordo com gravidade, mecanismo e incidência e a causalidade foi determinada. Em 240 pacientes, foram detectadas 11 RAM relacionadas ao tapentadol, sete ao viminol e três à dipirona isoladamente. Além disso, 22 RAM foram atribuídas a interações medicamentosas. As RAM, na sua maioria, foram leves, incomuns, possíveis e todas do Tipo A. As RAM induzidas pelo viminol foram associadas à idade, aumentando 6% o risco de RAM a cada ano de idade. No geral, os três analgésicos foram seguros, sendo a dipirona a mais segura. Na **etapa C**, o objetivo foi avaliar a eficácia e segurança do viminol por meio de revisão sistemática de literatura, utilizando-se a questão: "O viminol é mais eficaz e seguro que os inibidores da ciclooxigenase e analgésicos opioides em pacientes com dor aguda ou crônica?" A busca foi realizada em cinco bases de dados, sendo incluídos 14 artigos publicados entre 1969 e 1986. Os estudos totalizaram 2.353 pacientes, sendo o viminol administrado predominantemente por via oral na dose de 60 a 280 mg/dia em dose única, por, no máximo, 40 dias. Na maioria dos estudos, não houve diferenças significativas na eficácia em relação aos comparadores ativos, sendo o viminol bem tolerado. Os estudos apresentaram alto risco de viés e baixa certeza da evidência. Assim, novos estudos são necessários para orientar a sua escolha clínica.



**Palavras-Chave**: farmacovigilância; reações adversas a medicamentos; analgésicos.

## ABSTRACT

Analgesics are widely used, but the safety of dipyrone, viminol and tapentadol remains poorly understood. The objectives of this study were to transmit knowledge in pharmacovigilance (PV) for the implementation of a hospital service; evaluate adverse drug reactions (ADR) in the use of the three analgesics in a Pain Clinic and systematically review the safety and efficacy of viminol. In **stage A**, the objective was to evaluate the impact of PV training on hospital professionals. Before and after the training, the participant answered a questionnaire, counting the acquisition of knowledge in comparison to the gold standard answers. 129 professionals participated in the research. Before the training, everyone had some knowledge about PV, 7% had an average understanding, 93% revealed unsatisfactory understanding and none of the participants had satisfactory and complete understanding. The training was effective with an increase in spontaneous notifications. In **stage B**, the ADRs of the three analgesics were prospectively evaluated at the Santa Casa de Alfenas Pain Clinic. Patients were followed for up to 45 days, ADRs were reported and classified according to severity, mechanism, incidence and causality was determined. In 240 patients, 11 ADRs were detected related to tapentadol, seven to viminol and three to dipyrone alone. Additionally, 22 ADRs were attributed to drug interactions. The majority of ADRs were mild, uncommon, possible and all Type A. ADRs induced by viminol were associated with age, increasing the risk of ADRs by 6% with each year of age. Overall, the three analgesics were safe, with dipyrone being the safest. In **stage C**, the objective was to evaluate the efficacy and safety of viminol through a systematic literature review, using the question: “Is viminol more effective and safe than cyclooxygenase inhibitors and opioid analgesics in patients with acute or chronic?” The search was carried out in five databases, including 14 articles published between 1969 and 1986. The studies totaled 2,353 patients, with viminol administered predominantly orally at a dose of 60 to 280 mg/day in a single dose, for, at maximum, 40 days. In most studies, there were no significant differences in efficacy compared to active comparators, with viminol being well tolerated. The studies presented a high risk of bias and low certainty of the evidence. Therefore, new studies are needed to guide your clinical choice



**Keywords**: pharmacovigilance; adverse drug reactions; analgesics.

**SUMÁRIO**

## 1 INTRODUÇÃO GERAL

A Farmacovigilância (FV) monitora a segurança dos medicamentos no mercado, identificando novos eventos adversos desconhecidos durante os ensaios de aprovação (Crestan *et al*., 2020). Segundo a Organização Mundial de Saúde (OMS) (WHO, 2015), a FV possui como objetivos reconhecer precocemente possíveis Eventos Adversos a Medicamentos (EAM), dentre eles as Reações Adversas a Medicamentos (RAM), redefinindo informações relacionadas às suas suspeitas. Além disso, a FV promove a revisão das vantagens de uma terapia sobre a outra e comunica sobre a segurança do uso dos medicamentos. Para isso, é necessário que uma notificação de evento adverso alcance os órgãos regulatórios, espontaneamente pelos profissionais de saúde e/ou usuários de medicamentos, constituindo-se no método mais simples e barato (Montané; Santesmases, 2020), ou por meio de uma busca ativa em registros hospitalares e/ou relatos de pacientes (Li *et al*., 2018).

O conhecimento em FV torna as notificações espontâneas e busca ativa de EAM relevantes, podendo levar ao aparecimento de novos sinais (Fornasier *et al*., 2018). Esses sinais correspondem a informações reportadas sobre uma possível relação causal de um evento adverso e um fármaco (Dias; Ribeiro; Marques, 2014). As RAM, EAM muito comuns, podem resultar na não adesão ao tratamento proposto, comprometendo diretamente a qualidade de vida do paciente. Assim, detectar e minimizar a ocorrência dessas reações favorece as respostas clínicas, otimizando a farmacoterapia (Ribeiro *et al*., 2020).

A educação em FV é fundamental, já que as RAM constituem graves problemas de saúde e podem levar à sobrecarga dos serviços hospitalares. Sabendo-se que os profissionais de saúde possuem poucos conhecimentos sobre FV e notificações de RAM, é necessário capacitá-los, a fim de que possam adquirir um conjunto de competências para prescrever, distribuir e monitorar os medicamentos de forma racional (Reumerman *et al*., 2018). O desenvolvimento de ações em FV incrementa a adesão dos profissionais à notificação espontânea, levando à excelência dos tratamentos e segurança aos pacientes (Fernández *et al*., 2020).

Há uma preocupação crescente sobre os riscos associados a analgésicos (Knight *et al*., 2017). Neste contexto, a FV possibilita melhor atendimento ao paciente, ampliando a segurança em relação ao uso e fornecendo informações confiáveis para a avaliação efetiva do perfil risco-benefício desses medicamentos (WHO, 2006). Ao atuar na prevenção de EAM e identificação de RAM não detectadas anteriormente, a FV favorece a utilização segura e racional dos medicamentos, como os utilizados nas dores crônicas (Antimisiaris *et al*., 2017).

Considerando a utilização regional da Clínica da Dor da Santa Casa de Alfenas-MG, os três analgésicos mais indicados na dor crônica são a dipirona, viminol e tapentadol e que carecem de estudos relacionados à segurança e eficácia na população brasileira. O analgésico hidroxibenzoato de viminol possui estudos farmacológicos datados de 1977 (Neto; Murad; Monteiro, 1977). O cloridrato de tapentadol de liberação prolongada teve introdução recente no mercado brasileiro e o metamizol (dipirona) possui uso disseminado no Brasil. Assim, o levantamento das RAM associadas a esses três analgésicos permitirá a atuação efetiva da FV na promoção da saúde

Neste contexto, o objetivo geral deste trabalho foi transmitir o conhecimento para a promoção da FV, visando a interface pesquisa-extensão; avaliar as RAM no uso dos analgésicos dipirona, viminol e tapentadol na população atendida em um hospital regional; bem como avaliar a evidência científica sobre a segurança e eficácia do medicamento viminol em um contexto de saúde baseada em evidência. Os objetivos específicos do presente estudo foram promover a implantação de um serviço de FV em um hospital filantrópico do município de Alfenas-MG (ETAPA A), avaliar prospectivamente as RAM associadas à dipirona, viminol e tapentadol na Clínica da Dor integrante de um hospital regional (ETAPA B) e realizar uma revisão sistemática sobre a segurança e eficácia do viminol (ETAPA C).

# 2 REVISÃO LITERATURA / DESENVOLVIMENTO

## 2.1 FARMACOVIGILÂNCIA COMO ESTRATÉGIA NO USO RACIONAL DE MEDICAMENTOS

Na atual conjuntura, em que a inserção de novos medicamentos se tornou uma realidade, as ações em FV para a garantia da segurança e eficácia desses produtos são essenciais (Dylan *et al*., 2019), já que juntamente com os efeitos terapêuticos, são detectados efeitos indesejados (Wadhwa *et al*., 2021). O medicamento é a principal alternativa terapêutica na atenção à saúde, porém a sua utilização adequada requer muitos desafios, pois novos medicamentos trazem dificuldades à regulação sanitária devido às características de desenvolvimento e maior gravidade de EAM (Gellad; Kesselheim, 2017). Além disso, informações precisas sobre a segurança são obtidas apenas com o uso disseminado pela população (Pérez- Ricart *et al*., 2019).

Segundo OMS (2015), RAM é qualquer resposta prejudicial e não intencional a um medicamento, que ocorre em uma dose normalmente usada em humanos para profilaxia, diagnóstico, terapia ou para modificar uma função fisiológica. Já o EAM é qualquer ocorrência médica indesejável que pode aparecer durante o tratamento com um medicamento, sem necessariamente, possuir uma relação causal com este tratamento (Sousa *et al*., 2018). A FV é definida, de acordo com a RDC 406 (ANVISA, 2020) como a ciência que compreende atividades relativas à detecção, avaliação, compreensão e prevenção de EAM ou quaisquer outros problemas relacionados a medicamentos. Nos anos 60, com o desastre da Talidomida, o mundo conscientizou-se da necessidade de um efetivo mecanismo em FV. Desde então, a entrada de novos medicamentos no mercado vem acompanhado de monitorização, a fim de minimizar riscos (Silva *et al*., 2021).

As RAM aparecem em 10% dos pacientes ambulatoriais e são responsáveis por 5 a 10% das admissões hospitalares. Além disso, elas aparecem em 10-20% dos pacientes hospitalizados, o que aumenta o tempo de hospitalização. Na Europa, RAM foram consideradas a quinta causa de morte de pacientes hospitalizados, totalizando 197.000 mortes por ano e acarretando um gasto de 79 bilhões de euros para a sociedade (Montané; Santesmases, 2020). Diferentes estudos apontam que o índice de hospitalização por RAM pode chegar a 46% e causam até 2% das mortes hospitalares (González Rubio, 2018). Portanto, estudos norte americanos sustentam que as RAM estão entre as dez principais causas de morte nos Estados Unidos e são responsáveis por uma elevada carga financeira para os sistemas de saúde (Batel;

Marques, 2016). Existem vários fatores associados às RAM tais como: comorbidades, estado nutricional do paciente, idade, sexo, histórico de RAM, uso de vários medicamentos, dose administrada, fatores ambientais e sociais. Além disso, fatores relacionados ao mecanismo de ação do medicamento, orientação inadequada sobre o tratamento e prescrições incorretas também interferem no aparecimento desses eventos (Sousa *et al*., 2018).

Neste cenário, a FV pode contribuir para efetivas decisões regulatórias como revisão das bulas dos medicamentos, de acordo com a frequência e gravidade das RAM, bem como inclusão de novas indicações terapêuticas para o medicamento (Melo *et al*., 2021). Com a ação conjunta entre países e a alimentação de grandes bases de dados é possível a emissão de alertas em direção à segurança dos pacientes (Lacroix; Mallaret; Jonville-Bera, 2020).

Além dos profissionais de saúde, o envolvimento dos pacientes nas ações de FV favorece e fortalece o sistema (Van Hoof *et al*., 2022; Brown; Bahri, 2019). O surgimento de ferramentas inovadoras contribui significativamente para análise de dados e detecção de sinais, porém os grandes algoritmos não devem substituir o pensamento crítico e clínico do profissional (Hauben; Reynolds; Caubel, 2018). Dessa forma, a educação dos profissionais de saúde e usuários de medicamentos é a estratégia mais comum para o desenvolvimento da FV (Menang *et al*., 2023).

## 2.2 AS NOTIFICAÇÕES COMO FERRAMENTAS NA DETECÇÃO DE SINAIS

Terblanche e colaboradores (2018) afirmaram que há um crescimento na conscientização do impacto das RAM no atendimento ao paciente e na saúde pública. Dessa maneira, a implantação da FV, com treinamento adequado dos profissionais de saúde, reduz morbidade, mortalidade dos pacientes e custos futuros em instituições de saúde.

A notificação dos eventos é importante para a segurança do paciente, uma vez que a sua análise favorece a aprendizagem organizacional, identificando e evitando as causas, por meio da revisão e melhoria dos processos assistenciais (Furini; Nunes; Dalora, 2019). Essas notificações compreendem formulários que possuem dados sobre pessoas acometidas pelos EAM, informações sobre o paciente, descrição detalhada do evento adverso, administração de medicamentos concomitantes e dados de exposição (Bandekar; Anwikar; Kshirsagar, 2010). Dessa forma, as notificações de EAM apoiam os sinais em FV (Sartori *et al*., 2023). Diante disso, os órgãos reguladores devem focar na importância dessas notificações na consolidação das políticas em FV (Atia *et al*., 2021).

O método da notificação espontânea realizado pelos profissionais de saúde que lidam

diretamente com a prescrição, dispensação e administração dos medicamentos é o mais utilizado em FV (Modesto *et al*., 2016), apresentando a melhor relação custo-benefício para o monitoramento de RAM graves e raras (Mota; Vigo; Kuchenbecker, 2019). É o método mais barato, simples e utilizado para reconhecer novos problemas de segurança de medicamentos, sendo a subnotificação a sua principal limitação (Montané; Santesmases, 2020).

Neste contexto, a subnotificação continua sendo um dos principais problemas de FV (Khalili *et al*., 2020), já que apenas 1 a 10% das RAM são notificadas (González Rubio, 2018). Segundo Pepe e Novaes (2020), a taxa de notificação de EAM no Brasil está muito abaixo da recomendada pela literatura, que é de cerca de 300 notificações por milhão de pessoas, indicando problemas em gerar sinais de segurança à população.

Conforme Varallo *et al*. (2014), essa subnotificação está relacionada ao desconhecimento e à insegurança dos profissionais quanto às atividades de FV. De acordo com Salehi *et al*. (2020), reforçar o conhecimento de RAM durante a graduação e atividade profissional é uma importante abordagem para reduzir essa subnotificação. Além disso, o desinteresse em notificar dos profissionais de saúde relaciona-se à falta de tempo na rotina clínica. Um estudo de Moride *et al*. (1997) revela que profissionais da saúde, como médicos, tendem a selecionar os casos para a notificação espontânea, não reproduzindo a realidade dos índices de RAM. Portanto, a falta de sensibilização dos profissionais é um dos grandes impedimentos à notificação (Mulchandani; Kakkar, 2019). Al Meslamani (2023) acrescenta ainda como causas da subnotificação a falta de conhecimento sobre a gravidade, classificações e processos de notificação; falta de crença nas ferramentas de FV; de incentivo da liderança e do retorno e acompanhamento dos EAM notificados. Outro estudo de Varallo *et al*. (2018) mostrou que a subnotificação se relaciona também ao medo do profissional de envolver-se em ações judiciais, insegurança em relatar as RAM e complacência do profissional. Esse estudo ainda concluiu que o conhecimento da importância do relato de incidentes é uma motivação para aumentar a adesão dos profissionais ao monitoramento das RAM. Portanto, para Khan *et al*. (2022), notificar EAM é uma obrigação de todo profissional de saúde, bem como a capacitação nos assuntos inerentes à FV.

## 2.3 INTERVENÇÕES EDUCATIVAS EM FARMACOVIGILÂNCIA

O sistema de FV brasileiro, por meio da ANVISA (Agência Nacional de Vigilância Sanitária), em uma análise feita por Leal *et al*. (2019), é robusto e apresenta um bom nível de desempenho. Todavia, segundo Varallo *et al*. (2019), esforços devem estar voltados ao

treinamento de profissionais para notificar RAM e desvios de qualidade. A educação dos profissionais de saúde em FV é a abordagem mais comum para ampliar as atividades e fortalecer o sistema, favorecendo a detecção de sinais de risco (Menang *et al*., 2023).

O principal impacto das intervenções educativas é o aumento no número de notificações de EAM, como registrado no estudo de Ibrahim *et al*. (2021). Esses resultados são compartilhados por Bahnassi (2020) em que a educação contínua em FV melhora a prática e viabiliza o programa de segurança ao paciente. Foram verificadas lacunas no conhecimento em várias classes profissionais como farmacêuticos (Alshayban *et al*., 2020; Hadi *et al*., 2017; Kopciuch *et al*. 2019; Abdulsalim *et al*., 2023); enfermeiros (Adu-Gyamfi *et al*., 2022; Alan *et al*., 2013); radiologistas (AYDIN.*et al*., 2020); médicos (MUKATTASH *et al*., 2018) e dentistas (Diouf *et al*., 2013). Dessa forma, as estratégias educativas melhoram a gestão do risco de RAM, comprovadas pelos estudos de Panneerselvam, Kathirvelu, Manoharan (2022) e Shrestha *et al*. (2020) em que as intervenções educativas influenciaram positivamente nas atitudes dos profissionais em FV.

## 2.4 ANÁLISE DA CAUSALIDADE DE REAÇÕES ADVERSAS A MEDICAMENTOS

A análise da causalidade das RAM se mantém pouco frequente na prática clínica (Sartori *et al*., 2022). Isso pode estar relacionado à dificuldade de atribuir ao medicamento a causalidade das RAM em pacientes com múltiplas e crônicas doenças (Moses; Celi; Marshall, 2013).

Segundo Aguirre, García (2016), denomina-se imputabilidade a associação dos sinais e sintomas apresentados pelo paciente ao medicamento. Para definir essa relação causal, Bradford-Hill (1965) definiu a análise de alguns critérios como: a força de associação; consistência dos resultados; especificidade do efeito; sequência temporal; gradiente e plausabilidade biológica; coerência; experimentação e raciocínio por analogia.

Para avaliar essa causalidade e qualificar farmacoepidemiologicamente a interação entre os elementos envolvidos na RAM é muito utilizado na prática clínica os algoritmos de decisão validados (Aguirre; García, 2016), como os de Naranjo (1981), Jones (1982), Karch-Lasagna (1977), entre outros. A aplicação desses instrumentos apresenta a vantagem de padronização das análises e decisão mais objetiva da causalidade das RAM. No entanto, possuem limitações relacionadas à subjetividade das análises e dificuldade de preenchimento de alguns itens relacionados à retirada do medicamento suspeito e posterior reintrodução, já que raramente é realizado tal procedimento (Doherty, 2009).

O Centro de Monitoramento da Organização Mundial da Saúde-Uppsala (WHO-UMC)

(2005) propôs também o método de introspecção global, empregando-se uma escala que permite a avaliação da causalidade das RAM (certo, provável, possível, improvável, condicional/não classificado, sem avaliação/sem classificação). Por esse método, especialistas expressam um julgamento sobre a possível relação do medicamento à RAM considerando-se todos os dados disponíveis. Assim, a experiência do especialista (Rodrigues *et al*., 2018) e o detalhamento clínico-farmacológico do caso é fundamental para a avaliação dessa causalidade (Gupta; Kumar, 2017).

O terceiro e último método de avaliação da causalidade das RAM é o método probabilístico em que a probabilidade da ocorrência do evento é calculada a partir de uma estimativa anterior, calculada com base em relatórios de RAM e a estimativa posterior (Theophile *et al*., 2010).

Nenhum dos três métodos fornece uma estimativa confiável e precisa (WHO-UMC, 2005) e nenhum deles ainda foi aceito como padrão ouro (Shukla *et al*., 2021). Entretanto, nos estudos de Beniwal *et al*. (2019), a escala OMS-UMC foi considerada de fácil aplicação e utilização (Zorzela *et al*., 2018), sendo bem consistente, segundo Varallo *et al*. (2017), principalmente em ambientes hospitalares.

## 2.5 BUSCA ATIVA DE REAÇÕES ADVERSAS A MEDICAMENTOS NA MEDICINA DA DOR

Sabendo-se que a subnotificação é uma limitação da notificação espontânea, a busca ativa por RAM é uma alternativa (Hazell; Shakir, 2006). Esse método acaba indo ao encontro da RAM em um grupo definido e de forma contínua (Contreras-Salinas *et al*., 2021). Dessa forma, um conjunto de dados mais padronizados otimiza dados de EAM e favorece a vigilância pós-comercialização (Bailey *et al*., 2016).

Os sistemas de FV devem ser fortalecidos para que exista maior coordenação das autoridades regulatórias mundiais, a fim de avaliar e interpretar o custo-benefício dos analgésicos. Para isso, relatórios mais detalhados em ensaios clínicos dessa classe de medicamentos devem seguir diretrizes mais padronizadas e as RAM monitoradas e notificadas (Onakpoya; Heneghan; Aronson, 2018).

### 2.5.1 Dipirona

Há mais de um século a dipirona, conhecida como metamizol, é extensamente utilizada

na prática clínica pelas suas propriedades espasmolíticas, antipiréticas e analgésicas (Lutz, 2019). Porém, seu uso é banido em diferentes países devido ao risco de agranulocitose e neutropenia (Lerman *et al*., 2021). Seus efeitos adversos não são totalmente conhecidos devido à subnotificação (Preveden *et al*., 2022; Björnsson *et al*., 2020). Esse analgésico não opioide é uma alternativa a outros AINES (anti-inflamatórios não esteroidais) e ao paracetamol, sendo amplamente utilizado na dor aguda e crônica (Klose *et al*. 2020, Reist *et al*., 2018).

Apesar da existência de alguns estudos robustos, seu mecanismo de ação permanece controverso (Cury *et al*., 2011). Uma das primeiras evidências da ação da dipirona vem de um grupo de pesquisa brasileiro que propôs a participação do óxido nítrico no efeito antinociceptivo desse analgésico, estando associado à estimulação da via arginina/cGMP (Monofosfato cíclico de guanosina) em neurônios sensoriais (Duarte *et al*., 1992). Mais recentemente, Cecílio *et al*. (2020) evidenciaram que a dipirona está envolvida com a ativação molecular da cascata de sinalização PI3Kγ/AKT que promove a produção de óxido nítrico nos neurônios e consequente efeito analgésico. Além disso, considerado um AINE atípico por alguns autores, foi sugerido que seu efeito analgésico está relacionado à inibição central da enzima COX-3 (cicloxigenase) somando-se a sua ação nos sistemas canabinoides e opioides (Jasiecka; Maślanka; Jaroszewski, 2014). A inibição da COX-3, promove diminuição de PGE2 (prostaglandina) no sistema nervoso central (SNC), diminuindo a sensibilidade dos nociceptores (Chandrasekharan *et al*., 2002). Crunfli, Vilela, Giusti-Paiva (2015) avaliaram a participação da dipirona na sinalização do sistema endocarbinoide e verificaram que o antagonista canabinoide CB1 AM251 inibiu sua ação analgésica. Os autores sugeriram que com a inibição da enzima COX e da amidahidrolase de ácido graxo, há aumento da disponibilidade de ácido araquidônico, substrato para a síntese de endocarbinoides. Assim, com o incremento dessas substâncias, haveria estimulação dos receptores CB1 (canabinoide). Já Vázquez *et al*. (2005) verificaram que a utilização de naloxona (antagonista opioide) diminuiu a ação analgésica da dipirona, sugerindo efeito no sistema opioide. A dipirona está disponível em diversas formas farmacêuticas e apresentações, podendo ser a dose adulta máxima a ser administrada de quatro gramas diárias (dipirona [Bula]).

### 2.5.2 Hidroxibenzoato de viminol

O viminol é um analgésico sintético com estrutura diferenciada, sem qualquer relação química com outros analgésicos. É um derivado de pirriletanolamina que apresenta três carbonos assimétricos, o que faz com que o medicamento seja uma mistura racêmica de seis

estereoisômeros (Capretti; Frigerio, 1970; Shook; Kallman; Dewey, 1984). Os estudos disponíveis sobre este fármaco são muito antigos. Em 1984, ele foi descrito como um fármaco com potente atividade analgésica e mínimo risco de dependência (Shook; Kallman; Dewey, 1984). Em 1975, Albernaz *et al*. descreveram que o hidroxibenzoato de viminol era um medicamento seguro, pela incidência insignificante de eventos adversos, sendo considerado como atóxico por alguns autores (Albernaz *et al*., 1975).

Estudos experimentais de 1975 sugeriram que a redução da dor por esse fármaco estaria associada à depressão dos interneurônios presentes na lâmina V cerebral, no corno posterior da medula (Della Bella; Benelli; Besson, 1975). Em 1976, Della Bella, Benelli e Sassi sugeriram que o viminol possuía atividade analgésica pela interação com receptores opioides, visto que o uso da Naloxona antagonizava seus efeitos.

É comercializado apenas no Brasil, e apesar de ser aprovado pela ANVISA para o tratamento da dor, com a sua revalidação de registro datada de 1999 (ANVISA, 2023), a falta de estudos recentes sobre seu mecanismo de ação e especialmente, sobre sua eficácia e segurança, gera incerteza na tomada de decisão clínica. Está disponível na forma farmacêutica de cápsulas de 70 mg, em embalagens de 12 unidades, com o nome comercial de Dividol® (Dividol [Bula]).

### 2.5.3 Cloridrato de tapentadol

O tapentadol foi aprovado pelo FDA (*Food and Drug Administration*) nos Estados Unidos em 2008 para ser utilizado na dor aguda (moderada à grave) e, em 2011, sua forma de liberação prolongada foi aprovada para tratamento da dor crônica (Zajączkowska *et al*., 2018).

Em 2007, Tzschentke *et al*. caracterizaram o tapentadol como um fármaco inibidor da recaptação de noradrenalina e agonista de receptores μ opioides. Segundo Tzschentke *et al*. (2014), o tapentadol possui melhor tolerabilidade em comparação aos opioides clássicos, efeito que estaria relacionado à sua ação inibidora da recaptação de noradrenalina e atividade moderada nos receptores μ opioides, reduzindo, especialmente, náuseas, vômitos e constipação (Tzschentke, Christoph, Kögel, 2014). Suas propriedades analgésicas são inerentes de um único enantiômero que independe de ativação metabólica. Além disso, esse fármaco não mostrou potencial de indução e/ou inibição do citocromo P450 (Terlinden *et al*., 2007). Possui pouca ligação às proteínas plasmáticas e ausência de metabólitos ativos, tornando-o menos susceptível às interações medicamentosas e reações adversas delas provenientes (Guay, 2009). Atualmente é comercializado como Palexis LP® e está disponível na forma farmacêutica de comprimidos

revestidos de 50, 100, 150, 200 e 250 mg, em embalagens de 30 comprimidos (Palexis [Bula]).

# ETAPA A - EDUCAÇÃO EM FARMACOVIGILÂNCIA COMO FERRAMENTA NA CONSOLIDAÇÃO DO CONHECIMENTO DOS PROFISSIONAIS DE SAÚDE

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# EDUCAÇÃO EM FARMACOVIGILÂNCIA COMO FERRAMENTA NA CONSOLIDAÇÃO DO CONHECIMENTO DOS PROFISSIONAIS DE SAÚDE

# EDUCATION IN PHARMACOVIGILANCE AS A TOOL IN CONSOLIDATION OF THE KNOWLEDGE OF HEALTH PROFESSIONALS

# LA EDUCACIÓN EN FARMACOVIGILANCIA COMO HERRAMIENTA EN LA CONSOLIDACIÓN DEL CONOCIMIENTO DE LOS PROFESIONALES DE LA SALUD


## RESUMO

A Farmacovigilância (FV) atua na detecção, avaliação e prevenção dos diferentes eventos adversos a medicamentos. Um dos mecanismos para a constatação de riscos e atualização do perfil de segurança dos medicamentos é a notificação. Os sistemas de FV possuem como principal limitação a subnotificação que compromete a identificação correta de sinais. Muitos casos de subnotificação estão relacionados à insegurança de relatar um evento adverso pela falta de conhecimento dos profissionais de saúde. Este trabalho tem como objetivo avaliar o impacto de um treinamento em FV na percepção e habilidade dos profissionais de saúde de um hospital filantrópico. Imediatamente antes e após o treinamento, o participante respondeu a um questionário, contendo 12 questões dissertativas que apresentou respostas padrão ouro utilizadas para a avaliação do conhecimento em FV. Cada resposta foi compreendida entre 0 e 100%, sendo contabilizada a aquisição de conhecimento após a intervenção educativa. Participaram do treinamento 157 profissionais, dos quais 129 (82.2%) aceitaram participar da pesquisa, sendo 97 (75.2%) técnicos em enfermagem, 2 (1.5%) auxiliares de enfermagem e 30 (23.3%) enfermeiros. A maioria eram do gênero feminino e possuíam de 25 a 49 anos. Antes da capacitação, todos os participantes apresentaram algum conhecimento em FV e nenhum apresentou compreensão satisfatória e total; 93% revelaram compreensão insatisfatória e 7% mediana. Já após o treinamento, 30,2% apresentaram uma compreensão insatisfatória; 56,6% mediana; 12,4% satisfatória e 0,8% total. O treinamento foi efetivo com o incremento do número de notificações espontâneas. Porém, é preciso uma educação continuada, com o apoio da universidade, para que estes profissionais estejam sempre aptos a notificarem e atualizados em FV.


**Palavras-Chave:** Farmacovigilância. Reações adversas. Monitoramento de Medicamentos. Educação. Profissional de Saúde.


## ABSTRACT

Pharmacovigilance (PV) works to detect, evaluate and prevent different adverse drug events. One of the mechanisms for identifying risks and updating the safety profile of medicines is notification. PV systems have the main limitation of underreporting, which compromises the correct identification of signals. Many cases of underreporting are related to the insecurity of reporting an adverse event due to the lack of knowledge on the part of health professionals. This work aims to evaluate the impact of training in PV on the perception and skills of health professionals in a philanthropic hospital. Immediately before and after the training, the participant answered a questionnaire, containing 12 essay questions that presented gold standard answers used to assess knowledge in PV. Each response was between 0 and 100%,

accounting for the acquisition of knowledge after the educational intervention. 157 professionals participated in the training, of which 129 (82.2%) agreed to participate in the research, 97 (75.2%) nursing technicians, 2 (1.5%) nursing assistants and 30 (23.3%) nurses. The majority were female and aged 25 to 49. Before the training, all participants had some knowledge of PV and none had a satisfactory and complete understanding; 93% revealed unsatisfactory understanding and 7% average. After training, 30.2% had an unsatisfactory understanding; 56.6% median; 12.4% satisfactory and 0.8% total. The training was effective with an increase in the number of spontaneous notifications. However, continuing education is necessary, with the support of the university, so that these professionals are always able to report and be up to date in PV.

**Keywords**: Pharmacovigilance. Adverse reactions. Medication Monitoring. Education. Healthcare Personnel.

## RESUMEM

La Farmacovigilancia (FV) trabaja para detectar, evaluar y prevenir diferentes eventos adversos a los medicamentos. Uno de los mecanismos para identificar riesgos y actualizar el perfil de seguridad de los medicamentos es la notificación. Los sistemas de FV tienen como principal limitación la subregistro, lo que compromete la correcta identificación de las señales. Muchos casos de subregistro están relacionados con la inseguridad de reportar un evento adverso debido al desconocimiento por parte de los profesionales de la salud. Este trabajo tiene como objetivo evaluar el impacto de la formación en FV en la percepción y habilidades de los profesionales de la salud en un hospital filantrópico. Inmediatamente antes y después de la capacitación, el participante respondió un cuestionario que contenía 12 preguntas de ensayo que presentaban respuestas gold standard utilizadas para evaluar el conocimiento en FV. Cada respuesta estuvo entre 0 y 100%, representando la adquisición de conocimientos después de la intervención educativa. Participaron de la capacitación 157 profesionales, de los cuales 129 (82,2%) aceptaron participar de la investigación, 97 (75,2%) técnicos de enfermería, 2 (1,5%) auxiliares de enfermería y 30 (23,3%) enfermeros. La mayoría eran mujeres y tenían entre 25 y 49 años. Antes de la capacitación, todos los participantes tenían algún conocimiento sobre FV y ninguno tenía una comprensión satisfactoria y completa; El 93% reveló comprensión insatisfactoria y el 7% media. Después de la formación, el 30,2% tuvo una comprensión insatisfactoria; 56,6% mediana; 12,4% satisfactorio y 0,8% total. La formación fue eficaz y aumentó el número de notificaciones espontáneas. Sin embargo, es necesaria la formación continua, con el apoyo de la universidad, para que estos profesionales siempre puedan informar y estar al día en FV.

**Palabras clave**: Farmacovigilancia. Reacciones adversas. Monitoreo de Medicación. Educación. Personal sanitario:

## INTRODUÇÃO

Os medicamentos para que cheguem ao mercado, devem ter sua segurança e eficácia comprovados nos ensaios clínicos (LESLIE e SCHOUSBOE, 2019). Porém, devido às limitações e condições restritivas desses ensaios (FERMONT, 2019), o monitoramento dessa segurança e efetividade é realizado com notificações dos diferentes eventos adversos (SCHUTTE *et al.*, 2017). Dessa forma, a notificação constitui o elemento fundamental para a consolidação de um Sistema de Farmacovigilância (FV) (SHARIF *et al.*, 2022).

A FV enfrenta inúmeros desafios como a subnotificação e a baixa qualidade das mesmas, dificultando a detecção de um sinal (KIGUBA, OLSSON, WAITT, 2023; MARTIN, HANSSENS, PAUDYAL, 2018). Esses sinais correspondem a informações reportadas sobre uma possível relação causal de um evento adverso com um medicamento (DIAS, RIBEIRO e MARQUES, 2014). Assim, a escassez de conhecimento em FV, sem orientação a respeito de onde e como realizar notificações, estão entre as principais causas da subnotificação (TEKEL, BEKALU, SEMA, 2021). Neste contexto, existem lacunas no conhecimento dos profissionais da área de saúde que precisam ser preenchidas, a fim de melhorar a notificação dos Eventos Adversos a Medicamentos (EAM), já que as atitudes afetam diretamente as notificações e a prática de FV em ambiente hospitalar (SHRESTHA *et al.*, 2020; KIGUBA, OLSSON e WAITT, 2023). Dessa forma, durante a graduação, faz-se necessário conteúdo formativo e informativo voltado à FV, garantindo o uso seguro e racional de medicamentos na prática clínica futura (HERRERA COMOGLIO, 2020). Além disso, o treinamento contínuo, levando em consideração necessidades e preferências dos profissionais, é essencial para a consolidação da FV (GÜNER e EKMEKCI, 2019).

## OBJETIVO

Uma vez que há necessidade de uma formação integrada dos profissionais de saúde em FV (HASEN e HASHIM, 2021), o objetivo deste trabalho foi avaliar o impacto de um treinamento em FV na percepção e habilidade dos profissionais de saúde de um hospital filantrópico do Brasil.

## APROVAÇÃO ÉTICA

Este estudo foi aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal de Alfenas, Brasil (CEP), sob protocolo (CAAE 51321921.1.0000.5142) em 7 de dezembro de 2021.

## MÉTODOS

Foi realizado um treinamento em FV, presencialmente na sede de um hospital filantrópico de Alfenas-MG, em julho de 2022. Essa capacitação foi realizada pela farmacêutica da universidade com o apoio de alunos extensionistas. Todos os enfermeiros, técnicos e auxiliares de enfermagem da instituição foram convocados a participarem. Os demais profissionais de saúde foram apenas convidados. A capacitação, com duração média de 90 minutos, abordou a importância de detectar, avaliar/compreender e prevenir eventos adversos relacionados a medicamentos e a aplicabilidade da FV no contexto hospitalar, além disso, mostrou diferentes conceitos em FV que pertencem ao universo de eventos adversos. Adicionalmente, foi mostrado os objetivos e benefícios da FV, bem como os canais oficiais de notificação da Agência Nacional de Vigilância Sanitária (ANVISA), além do Centro de Farmacovigilância da UNIFAL-MG (CEFAL) da Universidade Federal de Alfenas (UNIFAL-MG). O CEFAL é um projeto vinculado à Pró-reitoria de Extensão da UNIFAL-MG que funciona como um facilitador no processo de notificação de EAM, por meio de notificações simplificadas. Assim, o profissional da saúde menciona o evento adverso em questão e o contato do paciente, cabendo ao CEFAL entrar em contato direto e realizar a notificação completa. Além disso, esse projeto envia e acompanha as notificações ao órgão regulador e às indústrias, fornecendo retornos aos pacientes e profissionais de saúde.

Imediatamente antes do treinamento, o participante, ao desejar participar da pesquisa, assinou o Termo de Consentimento Livre e Esclarecido (TCLE) e respondeu ao questionário

proposto, contendo 12 questões dissertativas, visando à avaliação do nível de informação acerca dos EAM e FV. Esse questionário, devidamente validado por Varallo, Planeta e Mastroianni (2017), apresentou respostas padrão ouro (Tabela 1) que foram utilizadas para a avaliação do conhecimento em FV de todos os participantes.

Tabela 1- Respostas padrão ouro para avaliação do conhecimento em FV

| Respostas padrão ouro | |
|---|---|
| **Pergunta** | **Resposta** |
| 1- O que é Farmacovigilância? | O monitoramento do uso de medicamentos para a detecção, avaliação e prevenção de reações adversas a medicamentos e quaisquer questões relacionadas ao medicamento. |
| 2- A prática da Farmacovigilância promove benefícios? Quando positivo, quais são os benefícios e quem são os beneficiários? | A prática da farmacovigilância promove benefícios para usuários de drogas, profissionais e instituições de saúde. Os benefícios incluem contribuir para a segurança do paciente, melhorar a qualidade do atendimento nas unidades de saúde e garantir que os medicamentos no mercado farmacêutico sejam seguros, eficazes e de alta qualidade. |
| 3- Quem pode notificar? | Usuários de drogas, profissionais de saúde e indústria farmacêutica. |
| 4- O que você pode notificar? | Quaisquer problemas relacionados a medicamentos, especialmente reações adversas a medicamentos, erros de medicação, ineficácia terapêutica e desvios de qualidade de medicamentos. |
| 5- a) O que você entende por evento adverso a medicamento? | Qualquer dano ou dano causado a pacientes decorrentes do uso de drogas. |
| b) O que você entende por reação adversa a medicamento? | Uma resposta a uma droga que é nociva e não intencional e que ocorre em doses normalmente usadas em humanos para profilaxia, diagnóstico, terapia de doença ou para modificações na função fisiológica. |
| c) O que você entende por Erros de medicação? | Qualquer evento evitável que possa causar ou levar ao uso inadequado de medicamentos ou danos ao paciente enquanto o medicamento estiver sob controle do profissional de saúde, paciente ou consumidor. |
| d) O que você entende por desvios de qualidade de medicamentos? | Um desvio dos parâmetros de qualidade estabelecidos para um produto ou processo. Em farmacovigilância, esses desvios podem incluir alterações organolépticas que são físico-químicas e/ou gerais (vazamentos, rotulagem inadequada, partículas estranhas, etc.) |
| e) O que você entende por suspeita de ineficácia terapêutica? | A ausência total ou parcial do efeito esperado do medicamento na condição de uso prescrita ou indicada na bula. |
| 6- Qual é a correlação entre farmacovigilância e segurança de medicamentos? | A prática da farmacovigilância, monitorando o uso de medicamentos, contribui para a regulação do mercado farmacêutico, pois foca na segurança, qualidade e eficácia desses produtos. |

| Respostas padrão ouro | |
|---|---|
| **Pergunta** | **Resposta** |
| 7- Como você explicaria por que uma droga não produz o efeito desejado? | O medicamento pode não produzir o efeito desejado por três motivos principais: as características inerentes ao paciente, erros de medicação e desvio de qualidade. |
| 8- Em quais etapas do uso de medicamentos podem ocorrer erros de medicação? | Em todas as etapas: prescrição, dispensação e administração. |

Fonte: Varallo, Planeta e Mastroianni (2017).

Cada resposta do participante foi comparada ao padrão ouro e sua nota foi compreendida entre 0 e 100%, conforme proposto por Varallo, Planeta e Mastroianni (2017). A avaliação foi realizada por dois pesquisadores de forma independente e o percentual médio de acerto de cada participante foi categorizado de acordo com o Tabela 2. Dessa forma, havendo compreensão total da temática com respostas semelhantes ao sugerido pelos autores, o participante recebia a porcentagem máxima.

Tabela 2- Categorização do nível de compreensão em FV de acordo com o percentual de acerto

| **Categorização do percentual de acerto** | |
|---|---|
| **Percentual de acertos** | **Nível de compreensão em FV** |
| X = 0% | Nenhuma compreensão |
| 0% < X < 50% | Compreensão insatisfatória |
| 50% ≤ X ≤ 75% | Compreensão mediana |
| 75% < X < 100% | Compreensão satisfatória |
| X = 100% | Total compreensão |

Fonte: Autores (2023).

Ao finalizar o treinamento, as questões foram novamente disponibilizadas aos participantes para uma análise e comparação das respostas obtidas antes e após, visando a avaliar a efetividade da capacitação na ampliação do conhecimento em FV.

Análise estatística

As análises estatísticas foram realizadas no programa R (R CORE TEAM, 2022), considerando um nível de significância nominal de 5%. O conhecimento dos profissionais de saúde quanto à FV foi estatisticamente comparado utilizando o teste pareado t de Student com averiguação da normalidade dos dados por meio do teste de Shapiro-Wilk.

## RESULTADOS

No total, participaram do treinamento 157 profissionais, dos quais 129 (82,2%) preencheram o TCLE e aceitaram participar da pesquisa ao responderem adequadamente os questionários propostos.

Dos 129 participantes da pesquisa, 97 (75,2%) eram técnicos em enfermagem, 2 (1.5%) auxiliares de enfermagem e 30 (23,3%) enfermeiros. Não houve participação de outras classes profissionais.

Com relação ao gênero, 108 (83,7%) eram femininos e 21 (16,3%) masculinos. Considerando-se a faixa etária dos participantes, a maioria apresenta de 25 a 49 anos, de acordo com o Tabela 3.

Tabela 3 – Categorização dos participantes do Hospital Filantrópico de Minas Gerais da capacitação em FV por faixa etária

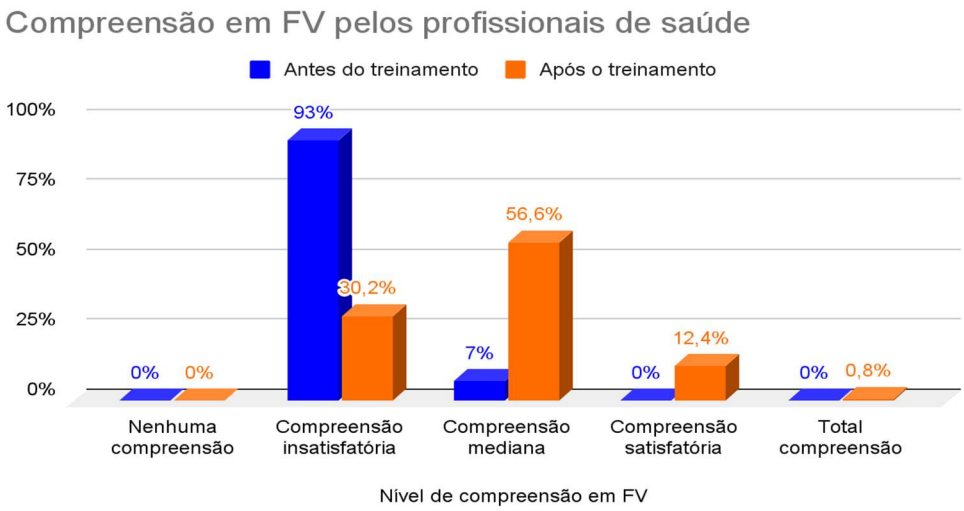
| Faixa etária | Número de profissionais |
|---|---|
| 20 a 24 | 6 |
| 25 a 29 | 14 |
| 30 a 34 | 15 |
| 40 a 44 | 14 |
| 45 a 49 | 15 |
| 50 a 54 | 5 |
| 55 a 59 | 1 |
| Não informou data de nascimento | 45 |

Fonte: Autores (2023).

Em relação a avaliação do conhecimento em FV, três participantes não tiveram incremento no conhecimento em FV, já 126 registraram um percentual de acerto superior após a capacitação

Antes da capacitação, todos os participantes apresentaram algum conhecimento em FV e nenhum apresentou compreensão satisfatória e total; 93% revelaram compreensão insatisfatória e 7% mediana. Já após o treinamento, 30,2% apresentaram uma compreensão insatisfatória; 56,6% mediana; 12,4% satisfatória e 0,8% total, conforme Figura 1.

Figura 1 – Distribuição do nível de compreensão dos participantes em FV antes e após a capacitação de um hospital filantrópico de Minas Gerais




Fonte: Autores (2023).

As porcentagens de acertos obtidas em ambos questionários, antes e após a capacitação em FV, apresentaram distribuição normal pelo teste Shapiro-Wilk ($p<0,05$). Pelo teste pareado t de Student pôde-se afirmar que estatisticamente existem diferenças entre as porcentagens de acertos antes e depois da capacitação em FV ($p<0,05$). Além disso, notou-se que a média da porcentagem de acertos antes da capacitação é igual a 29,2%, em que a nota mínima foi 4,2% e a nota máxima, 66,7%. Por outro lado, a porcentagem média de acertos após a capacitação foi 52,1%, sendo o valor mínimo igual a 10,4% e o valor máximo igual a 100,0%. Na tabela 4, pôde-se observar tais valores e ainda, a distribuição dos resultados, de modo que se pôde afirmar que antes da capacitação, 50% dos participantes obtiveram nota entre 18,7 e 37,5% e após a capacitação, a nota de 50% dos participantes compreenderam-se no intervalo entre 41,7 e 62,5%.

Tabela 4 - Percentuais de acertos classificados em quartis antes e após a capacitação.

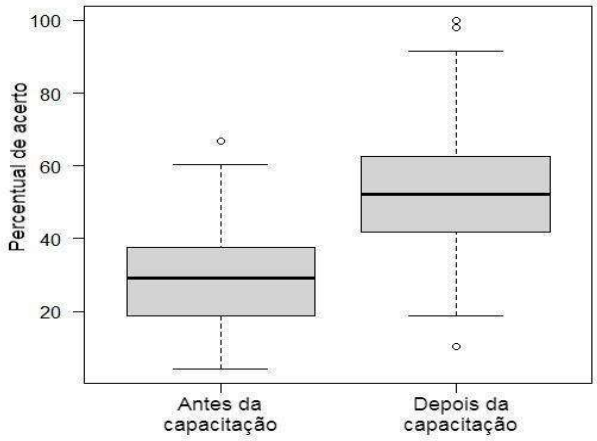
| | **Percentual de acerto antes da capacitação (%)** | **Percentual de acerto depois da capacitação (%)** |
|---|---|---|
| **Menor percentual de acerto registrado** | 4,2 | 10,4 |
| **1° Quartil** | ≤18,7 | ≤41,7 |
| **2° Quartil** | ≤29,2 | ≤52,1 |
| **3° Quartil** | ≤37,5 | ≤62,5 |
| **Maior percentual de acerto registrado** | 66,7 | 100 |

1° Quartil: representa 25% dos profissionais de saúde;
2° Quartil: representa 50% dos profissionais de saúde;
3° Quartil: representa 75% dos profissionais de saúde.

Fonte: Autores (2023).

Os dados também foram representados no formato *boxplot* com disposição vertical, de acordo com a Figura 2,

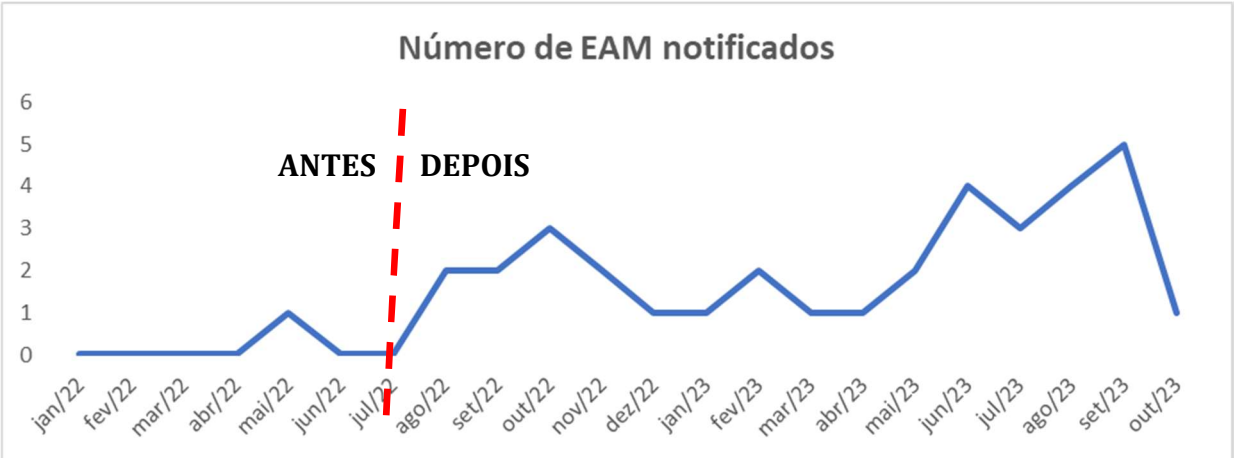
Figura 2 - Gráfico *boxplot* com os dados do percentual de acerto dos profissionais de saúde antes e após a capacitação.




Fonte: Autores (2023).

No período anterior ao curso de capacitação presencial, foi notificado apenas um EAM. Após a capacitação, o CEFAL já foram notificados até outubro de 2023, 33 RAM e um desvio de qualidade (FIGURA 3).

Figura 3- Número de notificações de EAM hospitalares antes e depois da intervenção educativa presencial no hospital filantrópico




Fonte: Autores (2023).

## DISCUSSÃO

Além dos órgãos regulatórios, as indústrias e demais instituições são responsáveis por estimular as notificações voluntárias, bem como enfatizar a sua importância para a manutenção da segurança e qualidade dos medicamentos (ATIA, BOTTO e ALARBI, 2021). A capacitação em FV promove redução na subnotificação de eventos adversos, que de acordo com Pal *et al.*. (2013), é a principal limitação para o abastecimento dos dados e consolidação dos sistemas de FV. Assim, obteve-se um aumento significativo das notificações dos diferentes eventos nesta instituição, como evidenciado nos estudos de Jusot el al (2020). Para sustentar esse resultado, a educação continuada para a implementação de atitudes em FV na prática clínica é fundamental (MUNSHI e MAURYA, 2023: ALBAYRAK e KARAHALIL, 2022), já que todas as atividades voltadas à FV são prejudicadas com a falta de treinamento dos profissionais de saúde (KIGUBA, OLSSON, WAITT, 2023). Portanto, de acordo com Chen *et al.,* (2021), o processo de aprendizagem favorece a aquisição de habilidades necessárias ao desenvolvimento de diferentes ações em FV. Outros autores ainda confirmaram que o desconhecimento e a falta de capacitação enquadram-se nas causas mais comuns de insucesso dos programas de implementação de FV institucionais, com a dificuldade de identificação dos diferentes EAM pelos profissionais de saúde (PRAVEEN *et al.,* 2012; SHARIF *et al.*, 2022; HEMA, BHUVANA e SANGEETHA, 2012).

Além da falta de conhecimento (SALEHI *et al.*, 2021), outro fator que prejudica a excelência do funcionamento dos sistemas de FV é o atraso na transmissão das notificações dos EAM aos bancos de dados dos órgãos regulatórios, como relacionado por Stegmann *et al.* (2022). Neste contexto, a proposta da adoção de notificações simplificadas *online*, bem como da responsabilidade de envio e retornos aos notificadores pelo CEFAL neste estudo, favorece a agilidade do abastecimento dos dados e promove praticidade aos profissionais de saúde, já que a falta de tempo e indisponibilidade de formulários de notificação, ausência de notificação *online* e falta de *feedbacks* são citados como fatores associados à subnotificação (SHARIF *et al.*, 2022; HUSSAIN *et al.*, 2022; THORNE *et al.*, 2018; GAHR *et al.*, 2021).

Em um estudo realizado por Hussain *et al.*. (2022), 55,3% dos profissionais enfermeiros relataram a falta de conhecimento sobre um centro nacional de FV e falta de tempo para notificar, enfatizando a notificação *online* como facilitador dessa atividade. Mediante isso, nesse treinamento realizado, foi demonstrado com detalhes, o processo de notificação nos sistemas informatizados nacionais, bem como a notificação junto ao CEFAL, como estratégia facilitadora de notificação. Além disso, o CEFAL garante o abastecimento do banco nacional de notificação que Jusot *et al.* (2020) estabeleceu ser uma grande dificuldade para os profissionais de saúde.

A taxa de retorno dos questionários neste estudo de 82,16% é concordante com os estudos de Sharif *et al.* (2022), em que dos 830 questionários propostos aos profissionais de saúde para avaliação do conhecimento em FV, 669 (80,6%) foram devolvidos e contabilizados. Os resultados obtidos também aproximaram-se aos de Abu Farha *et al.* (2018), cuja taxa de resposta foi de 75%.

A predominância da participação do gênero feminino também foi evidenciado por vários autores de diferentes países que também realizaram uma intervenção educativa em FV (SHRESTHA *et al.*. 2020, GANESAN *et al.*. 2017; TSUCHIYA *et al.*. 2019; HAJEBI *et al.*., 2010; HANAFI *et al.*., 2012; JOHN *et al.*., 2012; GUNER e EKMEKCI, 2019; ADU-GYAMFI *et al.*, 2022). A média de idade dos participantes do treinamento de 45 anos e a faixa etária predominante de 25 a 49 anos discordam dos resultados encontrados por Shrestha *et al.*. (2020)

que apresentaram média de 26 anos e predomínio da faixa etária de 21 a 30 anos dos participantes da capacitação em FV.

Os profissionais de saúde careceram de conhecimento inicial em FV e esse resultado também é compartilhado por Varallo, Planeta e Mastroianni (2017) e Abu *et al.*. (2018), cujos estudos mostraram conhecimentos insatisfatórios no pré-treinamento. Neste estudo, foi possível comprovar a efetividade de uma intervenção educativa na aquisição de conhecimentos em FV, corroborando com outros estudos conduzidos em diferentes países, incrementando significativamente o número de notificações de EAM (GUNER; EKMEKCI, 2019; HAJEBI *et al.*, 2010; HANAFI *et al.*., 2012; SAID e HUSSAIN, 2017; SHANKO e ABDELA, 2018; HU *et al.*, 2022).

Assim, a extensão universitária estando estruturada nas diretrizes da interação dialógica, interdisciplinaridade, interprofissionalidade e indissociabilidade favorece a transformação social (NOGUEIRA, 2000). Ao disseminar o conhecimento científico, compartilhando-os com profissionais de saúde, a universidade fortalece o elo com a comunidade (COSTA *et al.*, 2019). Dessa forma, esses profissionais devidamente capacitados, com o apoio da universidade, poderão alimentar os bancos de dados dos órgãos reguladores, possibilitando a identificação dos riscos e implementações de ações rumo à segurança dos medicamentos.

## CONCLUSÃO

O treinamento dos profissionais de saúde do hospital foi efetivo, mostrando que a maioria dos participantes tiveram incremento no conhecimento em FV após capacitação. Essa atividade extensionista melhorou o processo organizacional e favoreceu a segurança na utilização dos medicamentos. Porém, é preciso uma educação continuada, com o suporte universitário, para que estes profissionais estejam sempre aptos a notificarem eventos adversos e atualizados a respeito da FV, pois as intervenções educativas impactam positivamente no conhecimento em FV e em mudanças de postura pelos profissionais, possibilitando melhoria na segurança da utilização dos medicamentos.

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ETAPA B - COMPARATIVE SAFETY PROFILE OF METAMIZOLE, VIMINOL, AND TAPENTADOL: A PROSPECTIVE OBSERVATIONAL STUDY ON ADVERSE REACTIONS

**SUMMARY**

**Aim:** Given that the most potent analgesics used in clinical practice cause severe adverse effects and have a high potential for dependency, drugs such as metamizole (dipyrone), viminol and tapentadol can offer promising alternatives. Therefore, a recent safety assessment of these three medications is necessary, aiming to fill gaps in the literature and contribute to safer therapeutic strategies. The aim of this study was to prospectively assess adverse reactions associated with metamizole, viminol, and tapentadol in a pain management clinic.

**Methods:** Patients who had used metamizole, viminol, and/or tapentadol were followed up for 45 days via phone call. The information inherent to different adverse drug reactions (ADRs) was gathered and documented in the computerized systems of the Brazilian Health Regulatory Agency. ADRs were classified according to severity, mechanism, and incidence. Causality was determined.

**Results:** Among 240 patients, three adverse reactions to metamizole, seven to viminol, and 11 to tapentadol alone were documented. Additionally, 22 suspected adverse reactions were attributed to potential drug interactions among these analgesics and other medications. The ADRs were categorized as mild to moderate, type A, and common or uncommon. Causality was categorized as certain or possible. The results showed that ADRs induced by viminol were associated with age, with each year of age leading to a 6% increase in risk of adverse effects. No other association was found between tapentadol or viminol and sex, hypertension, arrhythmia, and anxiety and/or depression. It was not possible to analyze the metamizole data due to its low incidence. Overall, metamizole was the safest of the three analgesics evaluated.

**Conclusion:** These findings reinforce the safety profile of metamizole and its indication as a valuable therapeutic option for pain management, especially in patients at high risk for adverse reactions associated with other analgesics.

**Keywords:** Analgesics, Pharmacovigilance, Drug-Related Side Effects and Adverse Reactions, Drug Monitoring, Adverse Drug Reactions (ADRs), Safety Monitoring or Risk Management.

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## INTRODUCTION

Managing chronic pain presents a substantial challenge in clinical practice, primarily due to the significant adverse drug reactions (ADRs) often associated with prolonged analgesic use [1]. The effectiveness of analgesics largely depends on the pain's origin and type, and the safety of these drugs is not always well established. Non-opioid and opioid analgesics are frequently contraindicated for long-term use due to their associated risks: non-steroidal anti-inflammatory drugs (NSAIDs), the most common non-opioid analgesics, are linked to gastrointestinal tract injuries and hemorrhage [2], while opioids are known for their addictive properties [3].

The indiscriminate use of opioids has contributed to the global opioid crisis, underscoring the need for a more rational approach to medication use [4,5]. Alongside guidelines for appropriate pain medications [6], exploring alternative drugs that can either substitute or complement opioids to minimize their dosage is crucial. Metamizole a widely used analgesic in several countries, particularly in Latin America and much of the European Union [7,8], faces controversy due to risk of agranulocytosis and other serious adverse effects, to its ban in Sweden, the United Kingdom and the United States [9]. Despite its extensive use, metamizole is not listed in the World Health Organization's Model List of Essential Medicines [10], which also omits other analgesics like viminol and tapentadol. Viminol, approved by the Brazilian Health Regulatory Agency (ANVISA) since 1999 [14], is less studied, with limited evidence available from the 1970s and 1980s suggesting its efficacy and safety as an analgesic with minimal risk of addiction and adverse effects [15,16]. Tapentadol, approved by the FDA in 2008 for acute pain and in extended-release form in 2011 for chronic pain [11], is characterized as a norepinephrine reuptake inhibitor and a μ-opioid receptor agonist [12]. Its moderate μ-opioid receptor activity is thought to contribute to reduced nausea, vomiting, and constipation [13].

In this context, pharmacovigilance plays a critical role in ensuring the safety of analgesics use by monitoring drugs on the market and identifying new ADRs that may not have been detected during initial approval trials [17]. Pharmacovigilance aims to recognize potential adverse drug events (ADEs), including ADRs, and to redefine information related to their suspicions [18]. Thus, the aim to prospectively evaluate the ADRs associated with metamizole, viminol and tapentadol in a pain medicine clinic,

addressing key gaps in the literature and contributing to more informed therapeutic strategies.

## METHODS

The study employed an observational, analytical, longitudinal, and prospective design, conducted at the Pain Medicine Clinic of the Santa Casa Institution of Alfenas, Minas Gerais state, in the southeast region of Brazil (coordinates: 21.4255° S, 45.9477° W), from January 2022 to October 2023. Ethical approval was obtained from the Research Ethics Committee of the Federal University of Alfenas (UNIFAL-MG) (CAAE 51321921.1.0000.5142), and the study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19].

### Participants

A total of 240 participants were enrolled based on a sample size calculation using the binomial test for exact proportions, targeting a difference from the null hypothesis of 10% ADRs incidence. Under the null hypothesis of 0.1, the calculate sample size of 240 participants provided 95.2% power with a significance level of 4%. Eligible participants were 18 years or older, experiencing chronic pain, and had signed the Informed Consent Form (ICF) were considered eligible. All participants were undergoing mono or polydrug therapy with at least one of the study drugs – metamizole, viminol hydroxybenzoate, or tapentadol hydrochloride. Participants with acute pain, those who did not sign the ICF, and those who could not be contacted by telephone were excluded from the study.

### Experimental design

The study design is outlined in Figure 1. During routine consultations at the Pain Medicine Clinic, the responsible physician invited eligible participants. After signing the ICF, participants/guardians were contacted by phone five days later by members of the Pharmacovigilance Center of UNIFAL-MG (CEFAL). Participant information, including personal health history, and any ADEs, was collected using a standardized form from the VIGIMED® system (Figure 2), a computerized tool managed by ANVISA.

Participants who reported ADRs during the first contact were followed up within seven days to assess their clinical condition. If ADRs persisted or other ADEs were mentioned, the case was referred to the prescriber. Participants who did not report ADRs were contacted every 15 days for 45 days to monitor the potential onset of latent ADRs, as recommended by Els *et al*.. (2017) [20].

**Classification and causality of ADRs**

ADRs were categorized using the Medical Dictionary for Regulatory Activities [21]. ADRs related to metamizole, viminol, or tapentadol were classified by severity - mild (does not require drug treatment), moderate (requires hospitalization), or severe (requiring intensive care unit admission) [22] - and by mechanism of action as type A (dose-dependent, exaggerated effect) or type B (dose-independent, unpredictable) [23]. At the end of the proposed period, the frequency of ADRs was categorized as very common (≥10%), common (≥1% but <10%), uncommon (≥ 0.1% but <1%), and rare (≥0.01% but <0.1%) [24]. The presence and incidence of ADRs and the possible association with drug interactions were verified in the respective monographs, on the website drugs.com, and in the electronic clinical resource tool UpToDate®. To determine the causality of ADRs, a standardized scale from the World Health Organization-Uppsala Monitoring Centre (WHO-UMC, 2005) criteria was used [25]. Reactions were categorized as certain, probable, possible, unlikely, conditional, or unclassifiable. Causality was also determined based on the VIGIMED® questions required for the notification of ADEs and clinical judgment, considering the following criteria: temporality between the event and drug use; previous description of ADRs in scientific literature; the association between ADRs and the drug's mechanism of action, exclusion of confounding variables, and subjective and objective impressions of the prescriber [26]. CEFAL researchers were trained to standardize ADR causality assessments and were responsible for reporting and referring cases to the competent authorities.

**Statistical Analysis**

Descriptive statistics were applied to summarize population characteristics such as sex, age, race, primary diagnoses associated with pain, comorbidities, and incidence of

ADRs. Additionally, a descriptive survey of drug interactions and ADRs classification was conducted.

To assess the association between ADR occurrence and categorical variables, the Chi-square test was used. A significance level of 5% ($p<0.05$) was adopted to reject the null hypothesis.

The relationship between ADRs manifestation and sex was investigated using a Chi-square test of independence, while the association with age was analyzed using the T test. Logistic regression models were also performed to predict ADRs for each study drug, both in isolation and in drug interactions, with sex, age, and comorbidities as predictor variables.

## RESULTS

### Population Characteristic

Between January 2022 and October 2023, a total of 413 prescriptions were issued for 364 different individuals. Of these, 124 (34.07%) did not respond to follow-up calls, leaving 240 participants who agreed to take part in the study by signing the ICF and were contacted four times throughout the study.

Of the 240 participants, 35% (84) were male and 65% (156) female. The average age was 58.19 years. Among the participants, 25.83% (62) reported experiencing symptoms related to the administration of the study drugs (ADRs), with 67.74% (42) of these being female and 32.26% (20) male. Most participants identified as white (61.2%), while 17.74% identified as mixed-race, 9.68% as black, and 11.29% did not report their race. There was no significant association between ADR manifestation and sex ($\chi^2(1) = 0.14$; $p = 0.711$) or age ($t(91) = 1.39$; $p = 0.168$).

The primary diagnoses associated with pain among participants reporting ADRs were cancer-related pain 35.5% (22 participants); back pain (lumbar, cervical, and thoracic) 27.4% (17); osteoarthritis 12.9% (8); legs and feet pain 6.5% (4); fibromyalgia 4.8% (3); arthritis 3.2% (2); shoulders, arms, and forearms pain 4.8% (3); hip pain 3.2% (2); tendinitis 3.2% (2); and other conditions 9.67% (6).

The most frequent comorbidities were hypertension 16.1% (10 participants), hypertension combined with diabetes 14.5% (9), thyroid disorders 8.1% (5), depression

and anxiety 6.5% (4), heart disease 6.5% (4), diabetes 4.8% (3); respiratory disorders 4.8% (3), and other conditions 14.52% (9).

**Classification and Causality of ADRs**

Pregabalin, tapentadol, and viminol were the drugs most frequent associated with ADRs and drug interactions. These three medications alone accounted for 47.83%, 15.94%, and 10.15% of ADR occurrences, respectively (Table 1). Table 2 shows that 183, 147, and 105 drug interactions were detected for pregabalin, viminol, and tapentadol, respectively, when combined with other medications (drug interactions).

Focusing on the three analgesics under study, a total of 43 ADRs were detected among 22 participants, with 21 ADRs linked to a single drug and 22 resulting from drug interactions. A database analysis (monographs, drugs.com, UpToDate®) identified a total of 253 drug interactions involving these analgesics with other medications, however, only 22 (8.69%) of these interactions resulted in ADRs.

The incidence of ADRs for isolated tapentadol, viminol, and metamizole was 10.78% (11/102), 4.76% (7/147), and 1.60% (3/187), respectively (Table 3). For tapentadol, the ADRs were classified as mild or moderate (constipation and vomiting), type A, common or uncommon, and certain. For viminol, the ADRs were classified as mild or moderate (dizziness), type A, common (asthenia) or uncommon, and certain. For metamizole, the ADRs were classified as mild, type A, uncommon and certain (Table 3). It is important to highlight that no patient with ADR to metamizole presented with non-specific symptoms related to agranulocytosis, such as sore throat, fever and chills, ulcerative lesions in the mouth, gum inflammation, change in heartbeat, and muscle weakness.

Asthenia was the predominant complaint resulting from the interaction of viminol with other drugs. Among participants taking tapentadol, in addition to asthenia, somnolence was also a common adverse reaction, as shown in Table 4. For tapentadol, ADRs were classified as mild or moderate (mental confusion and dizziness; drowsiness and difficulty with motor coordination), type A, common or uncommon, and possible. For viminol, ADRs were classified as mild, type A, common or uncommon (tremor), and possible. No ADRs related to drug interactions were reported for metamizole (Table 4).

**Predictors Associated with ADRs**

A logistic regression analysis was conducted to identify predictors associated with the occurrence of ADRs for tapentadol and viminol, as shown in Table 5. Due to the low incidence of ADRs with metamizole, it was not possible to analyze the data for this drug. The results indicated that ADRs induced by viminol were significantly associated with age, with each additional year of age increasing the risk of adverse effects by 6%. No other significant associations were found between ADRs for tapentadol or viminol and factors such as sex, hypertension, arrhythmia, and anxiety and/or depression.

## DISCUSSION

Given the widespread use of analgesics, a significant number of ADRs are expected among users [27]. According to Jo *et al*.. (2021) [28], analgesics constitute the third class of medications with the highest rate of ADRs (4%), following antibacterials (20.3%) and antimycobacterials (5.4%). Similar results were observed by Sakuma *et al*.. (2020) [29], with 4.5% of their study population reporting ADRs related to analgesics, particularly among the elderly. The present study found that despite the frequent use of tapentadol and viminol, these drugs presented a relatively low incidence of ADRs. Among the three drugs studied, metamizole demonstrated the safest profile, corroborating findings from previous research and real-world evidence, as mentioned by Sznejder *et al*.. (2022) [30], which supported metamizole's safety in the Brazilian population.

Previous studies have consistently shown that ADRs are most frequent in female patients [31,32]. Franconi *et al*.. (2012) [33] reported that women have a 50 to 70% higher risk of experiencing ADRs, which may be attributed to differences in pharmacokinetics, pharmacodynamics, and hormonal factors. For instance, Lopes *et al*.. (2021) [34] demonstrated a significant disparity in opioid-related ADRs between the sexes, with 6.5% of female participants reporting ADRs compared to 3.4 of males. Tramadol, in particular, was associated with gastrointestinal, dermatological, and neurological ADRs in women. However, in contrast to these findings, the present study did not reveal any statistically significant influence of sex on ADR occurrence.

Comorbidities can play a crucial role in the development of ADRs [35]. In this study, 13 participants who experienced ADRs had comorbidities, such as hypertension and/or diabetes. The presence of comorbidities is often linked to polypharmacy, which increases the risk of drug-drug interactions and subsequent ADRs [36]. Polypharmacy,

combined with non-specific symptoms, presents a diagnostic challenge in identifying the exact cause of ADRs, highlighting the importance of detailed data collection and analysis [37]. It worth noting that while 253 drug interactions were detected across the three analgesics under investigation, only 22 (8.69%) were associated with ADRs. Tapentadol and viminol were most frequently implicated in drug interactions, yet these interactions did not result in significant clinical consequences, mirroring the findings of Riera *et al*.. (2022) [38], who also reported safe drug interactions involving analgesics without clinical implications.

Related to the drugs studied, metamizole emerged as the most prescribed, used, and tolerated analgesic. This is consistent with the results of Reist *et al*.. (2018) [39] who found that metamizole was the most frequently prescribed analgesic by anesthesiologists and pain specialists in German-speaking countries. The authors observed that 93.8% of 2,237 patients received metamizole, either alone (19.9%) or in combination with other analgesics (76.7%) for chronic pain management. Although they reported a 3.5% incidence of metamizole-associated agranulocytosis, it was not possible to definitively attribute the agranulocytosis to metamizole, as patients were also using other medications. Indeed, various drugs, including antipsychotic, antibiotic, antithyroid agents, and antiplatelet medications, have been implicated in agranulocytosis [40]. Moreover, studies evaluating agranulocytosis related to metamizole often fail to clearly distinguish between neutropenia, agranulocytosis, and aplastic anemia [41]. Lobo *et al*.. (2013) [42] found that 20% of ADRs reported in a hospital in northern Brazil were linked to metamizole, but did not specify the nature of these effects, attributing the high incidence to the frequency of metamizole use in the study population. The ADRs identified in this study - namely asthenia, hypotension, and gastric discomfort - were not reported in previous studies, though they were mild and consistent with the drug's label. Despite its demonstrated safety, as noted by Sznejder *et al*.. (2022) [30], which supported metamizole’s safety in the Brazilian population, metamizole remains banned in many countries, potentially due to geopolitical factors rather than scientific evidence

Viminol, on the other hand, lacks recent studies on its efficacy and safety. Between 1985 and 2019, only 20 ADRs related to viminol were reported in the Americas, with symptoms including dizziness, abdominal pain, nausea and vomiting, malaise, asthenia, withdrawal syndrome, ataxia, coma, peripheral neuropathy, mental confusion, dyspnea, urticaria, and skin tissue disorders. The majority of ADRs are manifested in males, in young adults, aged between 18 and 44 years [43]. Historical studies, such as

those by Foschi *et al*.. (1985) [44] observed sedation as an ADRs related to viminol, while Martinetti *et al*.. (1970) [45] reported dizziness and sedation, and Frigerio *et al*.. (1974) [46] asthenia, dizziness, and skin rashes. In the current study, dizziness, drowsiness, asthenia, tremors, and skin rashes were the most frequently reported ADRs, observed in both male and female participants with a mean age of 65.2 years. Importantly, this is the first study to highlighted that in participants over 55 years of age, each additional year increased the risk of ADRs by 6%, underscoring the need for cautious prescription in older adults.

Tapentadol was the analgesic most frequently associated with ADRs in this study. Previous meta-analyses have demonstrated that tapentadol is generally safe, with constipation being the most commonly reported ADRs [47]. Abeyaratne *et al*.. (2018) [48] also identified gastrointestinal issues as common, but reported that psychiatric disorders constituted 50% of tapentadol-related. Coluzzi and Ruggeri (2014) [49] found that tapentadol prolonged-release formulations reduced ADR-related discontinuations compared to oxycodone/naloxone. In a study by Mateos *et al*.. (2021) [50] involving 81 patients with chronic knee and lower back pain, 18.1% of patients experienced ADRs likely related to extended-release tapentadol and 8.4% discontinued treatment due to ADRs.

Monitoring and reporting ADRs during analgesic treatment are critical for improving pain management and patient outcomes [51]. Studies like the present one reinforce pharmacovigilance efforts by providing essential data to support regulatory agencies' decision-making. Many medications, including analgesics, have been withdrawn from the market due to safety concerns, often without a systematic investigation to establish a clear cause-effect relationship for ADRs [52.53]. Pharmacovigilance also plays a key role in strategies such as including drugs in the World Health Organization's list of essential medicines, where safety data help determine the optimal cost-benefit ratio. The findings of this study suggest that analgesics like metamizole could be strong candidates for inclusion in this list, especially in resource-limited settings where safe and effective pain management options are crucial.

## CONCLUSION

The results of this study clearly demonstrate that metamizole, viminol, and tapentadol are safe analgesics, with a low incidence of adverse drug reactions (ADRs)

and no severe side effects reported. This prospective assessment addresses significant gaps in the literature by providing current safety data on these three analgesics in a clinical setting. Among the three, metamizole emerged as the safest and most frequently prescribed, making it a valuable option for pain management, particularly in settings where the need for non-opioid, low-risk analgesics is critical. Viminol and tapentadol also exhibited favorable safety profiles, supporting their inclusion in therapeutic protocols for both acute and chronic pain. These findings highlight the potential of these drugs to serve as safer alternatives or adjuncts to analgesics with higher ADR rates and dependency risks, and underscore the importance of further studies to inform clinical practice and regulatory decisions.

## DISCLOSURE OF INTEREST

The authors declare that they have no competing interests.

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**Table 1.** Frequency of Isolated Drugs Related to Adverse Drug Reactions (ADRs) in Patients of the Pain Medicine Clinic.

| DRUG | FREQUENCY | RELATIVE FREQUENCY | CUMULATIVE FREQUENCY |
|---|---|---|---|
| Pregabalin | 33 | 47.83% | 33 (47.83%) |
| Tapentadol | 11 | 15.94% | 44 (63.77%) |
| Viminol | 7 | 10.14% | 51 (73.91%) |
| Duloxetine | 6 | 8.70% | 57 (82.61%) |
| Metamizole | 3 | 4.35% | 60 (86.96%) |
| Tramadol | 3 | 4.35% | 63 (91.30%) |
| Topiramate | 2 | 2.90% | 65 (94.20%) |
| Indomethacin | 1 | 1.45% | 66 (95.65%) |
| Escitalopram | 1 | 1.45% | 67 (97.10%) |
| Quetiapine | 1 | 1.45% | 68 (98.55%) |
| Tizanidine | 1 | 1.45% | 69 (100.00%) |

**Table 2.** Frequency of Drug Interactions in Patients of the Pain Medicine Clinic.

| DRUG | FREQUENCY | RELATIVE FREQUENCY | 95% CI FREQUENCY |
|---|---|---|---|
| Pregabalin | 183 | 76.25% | (69.62%; 80.79%) |
| Viminol | 147 | 61.25% | (54.26%; 66.88%) |
| Tapentadol | 105 | 43.75% | (37.10%; 49.89%) |
| Duloxetine | 17 | 7.08% | (4.27%; 11.21%) |
| Escitalopram | 3 | 1.25% | (0.32%; 3.88%) |
| Amitriptyline | 3 | 1.25% | (0.32%; 3.88%) |
| Buprenorphine | 3 | 1.25% | (0.32%; 3.88%) |
| Alprazolam | 2 | 0.83% | (0.14%; 3.28%) |
| Sertraline | 2 | 0.83% | (0.14%; 3.28%) |
| Metoprolol | 2 | 0.83% | (0.14%; 3.28%) |
| Tizanidine | 2 | 0.83% | (0.14%; 3.28%) |
| Methadone | 2 | 0.83% | (0.14%; 3.28%) |
| Furosemide | 2 | 0.83% | (0.14%; 3.28%) |
| Lactulose | 1 | 0.41% | (0.02%; 2.64%) |
| Hidroclorothiazide | 1 | 0.41% | (0.02%; 2.64%) |
| Omeprazole | 1 | 0.41% | (0.02%; 2.64%) |
| Nimesulide | 1 | 0.41% | (0.02%; 2.64%) |
| Pantoprazole | 1 | 0.41% | (0.02%; 2.64%) |
| Espironolactone | 1 | 0.41% | (0.02%; 2.64%) |
| Nebivolol | 1 | 0.41% | (0.02%; 2.64%) |
| Metamizole | 1 | 0.41% | (0.02%; 2.64%) |

**Table 3.** Adverse Drug Reactions (ADRs) Associated with Isolated Tapentadol, Viminol, and Metamizole in Patients of the Pain Medicine Clinic.

| ADRs | N (%) | 95% CI Frequency | Severity | Mechanism of action | Incidence* | Causality |
|---|---|---|---|---|---|---|
| **TAPENTADOL** | | | | | | |
| Anorexia | 2 (18.18%) | [3.21%; 52.25%] | Mild | Type A | Common | Certain |
| Lip paresthesia | 2 (18.18%) | [3.21%; 52.25%] | Mild | Type A | Common | Certain |
| Blurred vision | 2 (18.18%) | [3.21%; 52.25%] | Mild | Type A | Common | Certain |
| Constipation | 1 (9.09%) | [0.48%; 42.88%] | Moderate | Type A | Uncommon | Certain |
| Lack of concentration | 1 (9.09%) | [0.48%; 42.88%] | Mild | Type A | Uncommon | Certain |
| Restlessness | 1 (9.09%) | [0.48%; 42.88%] | Mild | Type A | Uncommon | Certain |
| Somnolence | 1 (9.09%) | [0.48%; 42.88%] | Mild | Type A | Uncommon | Certain |
| Vomiting | 1 (9.09%) | [0.48%; 42.88%] | Moderate | Type A | Uncommon | Certain |
| **VIMINOL** | | | | | | |
| Asthenia | 3 (42.86%) | [11.81%; 79.76%] | Mild | Type A | Common | Certain |
| Rash | 1 (14.29%) | [0.75%; 57.99%] | Mild | Type A | Uncommon | Certain |
| Somnolence | 1 (14.29%) | [0.75%; 57.99%] | Mild | Type A | Uncommon | Certain |
| Dizziness | 1 (14.29%) | [0.75%; 57.99%] | Moderate | Type A | Uncommon | Certain |
| Tremors | 1 (14.29%) | [0.75%; 57.99%] | Mild | Type A | Uncommon | Certain |
| **METAMIZOLE** | | | | | | |
| Asthenia | 1 (33.33%) | [1.77%; 87.47%] | Mild | Type A | Uncommon | Certain |
| Epigastric discomfort | 1 (33.33%) | [1.77%; 87.47%] | Mild | Type A | Uncommon | Certain |
| Hypotension | 1 (33.33%) | [1.77%; 87.47%] | Mild | Type A | Uncommon | Certain |

* Incidence calculated considering the 102 patients who received tapentadol; 147 patients who received viminol; and 187 patients who received metamizole.

**Table 4.** Adverse Drug Reactions (ADRs) Related to Drug Interactions of Tapentadol and Viminol in Patients of the Pain Medicine Clinic.

| ADRs | N (%) | 95% CI Frequency | Severity | Mechanism of action | Incidence* | Causality |
|---|---|---|---|---|---|---|
| **TAPENTADOL** | | | | | | |
| Asthenia | 3 (2.86%) | [0.74%; 8.73%] | Mild | Type A | Common | Possible |
| Somnolence | 3 (2.86%) | [0.74%; 8.73%] | Mild | Type A | Common | Possible |
| Sweating and cold extremities | 2 (1.90%) | [0.33%; 7.38%] | Mild | Type A | Common | Possible |
| Mental confusion and dizziness | 1 (0.95%) | [0.05%; 5.96%] | Moderate | Type A | Uncommon | Possible |
| Constipation | 1 (0.95%) | [0.05%; 5.96%] | Mild | Type A | Uncommon | Possible |
| Epigastric discomfort | 1 (0.95%) | [0.05%; 5.96%] | Mild | Type A | Uncommon | Possible |
| Dyspnea | 1 (0.95%) | [0.05%; 5.96%] | Mild | Type A | Uncommon | Possible |
| Drowsiness and difficulty with motor coordination | 1 (0.95%) | [0.05%; 5.96%] | Moderate | Type A | Uncommon | Possible |
| Dizziness | 1 (0.95%) | [0.05%; 5.96%] | Mild | Type A | Uncommon | Possible |
| **VIMINOL** | | | | | | |
| Asthenia | 3 (2.04%) | [0.53%; 6.31%] | Mild | Type A | Common | Possible |
| Somnolence | 2 (1.36%) | [0.24%; 5.33%] | Mild | Type A | Common | Possible |
| Dizziness | 2 (1.36%) | [0.24%; 5.33%] | Mild | Type A | Common | Possible |
| Tremor | 1 (0.68%) | [0.04%; 4.30%] | Mild | Type A | Uncommon | Possible |

* Incidence calculated considering the 102 patients who received tapentadol; and 147 patients who received viminol.

**Table 5.** Predictors Associated with Adverse Drug Reactions (ADRs) of Tapentadol and Viminol.

| CARACTERISTIC | OR | 95% CI Frequency | P value |
|---|---|---|---|
| **TAPENTADOL** | | | |
| Sex | | | |
| F | — | — | |
| M | 0.70 | 0.19; 2.29 | 0.6 |
| Hypertension | | | |
| No | — | — | |
| Yes | 0.41 | 0.08; 1.72 | 0.2 |
| Diabetes | | | |
| No | — | — | |
| Yes | 2.16 | 0.38; 11.20 | 0.4 |
| Arrhythmia | | | |
| No | — | — | |
| Yes | 0.84 | 0.04; 5.84 | 0.9 |
| Anxiety and/or depression | | | |
| No | — | — | |
| Yes | 0.46 | 0.10; 1.66 | 0.3 |
| Age | 0.98 | 0.93; 1.02 | 0.3 |
| **VIMINOL** | | | |
| Sex | | | |
| F | — | — | |
| M | 0.85 | 0.20; 3.13 | 0.8 |
| Hypertension | | | |
| No | — | — | |
| Yes | 1.53 | 0.39; 6.13 | 0.5 |
| Diabetes | | | |
| No | — | — | |
| Yes | 0.31 | 0.02; 1.94 | 0.3 |
| Arrhythmia | | | |
| No | — | — | |
| Yes | 0 | | >0.9 |
| Anxiety and/or depression | | | |
| No | — | — | |
| Yes | 0.78 | 0.19; 2.79 | 0.7 |
| Age | 1.06 | 1.00; 1.12 | 0.041 |

OR: Odds Ratio

**Figure legends:**

**Figure 1.** Experimental design - contact with the patients via phone call according to the manifestation of ADRs.

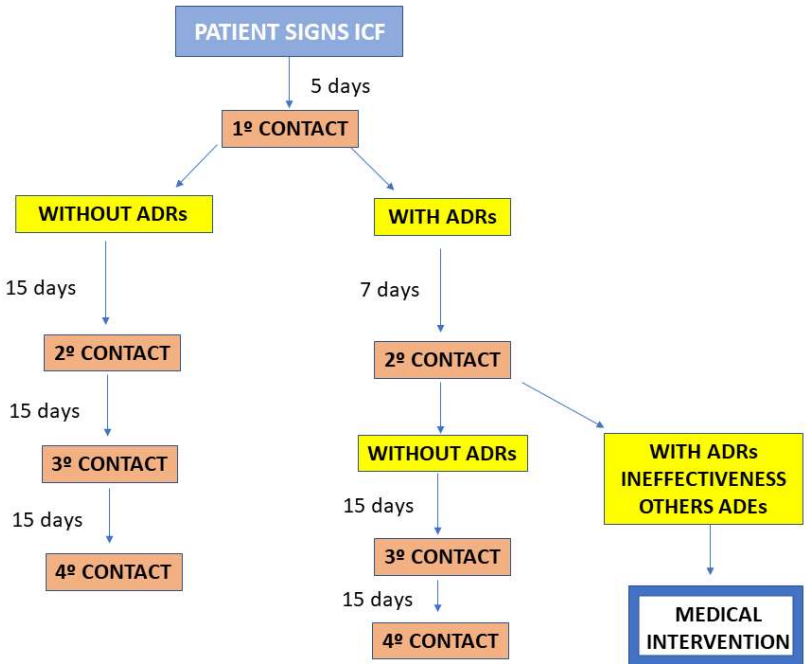


**Figure 2.** VIGIMED® form for notification of ADRs.

**MEDICATION USER DATA**
1- Full name
2- Gender
3- Weight
4- Date of birth
5- Age at time of ADR
6- Color or race
7- Height
8- Country
9- Municipality of residence
10- Hospitalized ( ) yes ( ) No
11- Health problems and personal history
12- User email
13- User phone

**MEDICINE DATA**
1- Name of the medicine
2- Lot
3- Expiration date
4- Treatment start date
5- Continuation of treatment ( ) yes ( ) No
6- Manufacturer industry
7- Description of ADR
8- ADR start date
9- ADR end date
10- Consequence of ADR
( ) Death
( ) Life risk
( ) Persistent or significant disability
( ) Caused or prolonged hospitalization
( ) Anomaly or malformation of the newborn
( ) Other clinically important situations
( ) Not applicable
11- Communication to the industry about what happened ( ) yes ( ) No
12- ADR disappeared or improved after drug withdrawal ( ) yes ( ) No
13- ADR reappeared after drug reintroduction ( ) yes ( ) No
14- Use other medications ( ) yes ( ) No Which _____

# ETAPA C - EFFECTIVENESS AND SAFETY OF VIMINOL IN PAIN TREATMENT: A SYSTEMATIC REVIEW

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**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

**SIGNIFICANCE**

Viminol is an analgesic used in clinical practice, whose pharmacological studies date back to the 1970s. Therefore, this review provides evidence of its safety and effectiveness that justifies or not the replacement of other analgesics with this ancient medication.

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**ABSTRACT**

Although viminol is approved and used in practice, there is a lack of recent scientific evidence, as its pharmacological studies date back to the 1970s. Therefore, the objective of this review was to evaluate the effectiveness and safety of viminol to support clinical decision-making. The review was performed according to the following question: “Is viminol more effective and safer than other analgesics in the treatment of acute or chronic pain?”, outlined through the PICOS strategy. The search was performed in five databases. Randomized clinical trials with adult patients with acute or chronic pain were included, with safety and effectiveness as outcomes. In total, 14 articles were included in this review, two of which were eligible through the databases and 12 through manual search. These are old studies and totaling 2,353 patients. Viminol was predominantly administered orally at a dose of 60 to 280 mg/day in a single dose, for a maximum of 40 days of treatment. In some studies, viminol was more effective than placebo, in others, more effective than the reference, but in the vast majority, without significant differences. Overall, it was well tolerated. However, all included studies had a high risk of bias and the certainty of evidence for the outcomes analyzed was very low. Studies on viminol in pain are old and lack methodological rigor to improve the robustness of the evidence generated. Therefore, there is a lack of more recent and complete studies to guide the clinical choice of viminol.

**Keywords:** Dividol. Drug effects. Drug-Related Side Effects and Adverse Reactions. Viminol

## INTRODUCTION

Pain treatment poses a clinical challenge, as the currently available drugs are not universally effective for various types of pain (1). In 1986, the World Health Organization (WHO) proposed the cancer pain analgesic ladder (2). The ladder involves the use of

cyclooxygenase inhibitors for the treatment of mild pain, weak opioids for the treatment of moderate pain, and potent opioids for the treatment of severe and persistent pain. Non-opioid analgesics and adjuvants, such as antidepressants and antiepileptics, can also be used in the treatment of moderate to severe pain (3). Although opioids are highly effective in pain management, their use is associated with severe adverse effects, including the risk of addiction (4,5). Globally, the use of opioids has resulted in 480,000 deaths, with opioids being implicated in the fatalities of 120,000 individuals (2). In addition to guidelines for the appropriate prescription of analgesics (6), it is important to examine alternative therapeutic strategies for pain treatment.

Viminol (Dividol®) is a drug indicated for acute and chronic pain, sold only in Brazil, where it was approved in 1974 by the National Health Surveillance Agency (6). In Italy, the drug was approved and commercialized in 1971, but in 2010 the Italian Drug Agency ended the authorization since the manufacturer did not request renewal (7). Because of its unusual chemical structure, viminol is not classified as an opioid or COX inhibitor drug (8). Shook *et al*.. (1983) promoted the isolation and characterization of viminol stereoisomers and evaluated its effect in rats. The authors suggests that viminol had a central analgesic activity provided by a tertiary amine group and an adrenergic effect associated with a secondary amine group (9). Studies have shown that viminol presents a low risk of addiction both in animals (10) and humans (11–14).

Despite the authorization for the commercialization of viminol in Brazil, there is limited data on its effectiveness and safety. The studies that evaluate the effectiveness and safety of viminol are from the 1970s and early 80s. Therefore, this systematic review aims to evaluate the effectiveness and safety of viminol to synthesize evidence that supports clinical decision-making regarding the use of this medication.

## RESULTS

### Study selection

Fourteen articles were retrieved from the databases. After removing the duplicates, six were left. Through screening and eligibility, four articles were rejected. The two remaining articles were read in full and included in this systematic review. The Kappa coefficient was 1.0, which represents perfect agreement between the researchers. Twelve studies were added from the manual search, totaling 14 articles, as illustrated in the PRISMA diagram (Figure 1).

### Study characteristics and outcomes

Table 1 presents the main characteristics of each study. These are old studies dating mostly from the 1970s, with one of the studies dating back to 1969 (15), the two most recent being published in the 1980s (16,17). Most studies were double-blind and crossover. A single study was described as multicenter involving a larger number of participants (1,791) (11), while the others were performed with a very restricted number (from 6 to 93) of patients. In total, 2355 patients were included in the studies, predominantly female and aged between 20 and 74 years. In four studies the authors did not report the ages of the participants (11,18–20). Among the included studies, most focused on chronic pain, with moderate to severe intensity (13,17,19–22). The studies related different diseases and procedures, such as cervical syndromes (18); leprosy (23); neoplasms (11,12,19,21); postpartum pain (13,16,17,20,22); osteoarticular, peripheral vascular, traumatic, dental, and visceral origin pain (11); skeletal, articular, neural, visceral, and obstructive arterial pain, and headache (12); cholecystectomy, gastrectomy, and hemicolectomy (17); rheumatoid arthritis, coxitis, and lower limbartheriosclerosis obliterans (21); tuberculosis (24); osteoarthritis (15); neck pain, cervic-brachialgia, backache, lumbo-sciatica, and trigeminal neuralgia (25).

Table 2 shows the treatment characteristics. The oral dose of viminol ranged from 60 to 400 mg/day, the intravenous dose was administered from 2.5 to 10 mg, while the rectal dose used was 100 mg. Viminol was used in a single oral dose in most studies. It was used three times a day, for a maximum of 40 days of treatment in seven studies: 40 days (18), 21-28 days (23), 5 days (19), 1-3 days (12), 30 days (24), 1-4 days (15) and 10 days (25). Viminol was also used every four hours for up to five days in two studies (15,19).

Table 3 exhibits the effectiveness and safety of the treatment. To assess pain remission, six studies measured pain before and after drug intervention, using different scales (12,15–17,21,22). Seven of the included studies assessed pain by qualitative methods (18–20,22–25), five studies employed a numerical rating scale (12,15–17,21) and two studies evaluated a pain remission scale (11,13). Viminol was successful compared to placebo in nine studies (11–13,16–19,22,25). The results showed that viminol was more effective than propoxyphene (11). According to Moroni *et al*.. (1978), viminol associated with chlordiazepoxide was more effective than the use of these drugs alone (21). No significant difference was observed in the analgesic effect of viminol compared with pentazocine (16,17), codeine (12,13,15) and aminopyrine (15). Viminol was less effective compared to pentazocine (20), and dipyrone (22).

The main adverse effects reported with the use of viminol were drowsiness, dry mouth, nervousness, sweating, nausea (17), heartburn, vomiting, sedation, feeling hot, dizziness, nausea (12) and gastric disturbances with high doses of viminol (19). Frigerio *et al*.. (1974), described a lower incidence of vertigo and drowsiness associated with viminol when compared to propoxyphene (11). Hennay *et al*.. (1977) reported a single incidence of drowsiness and sensation of heat associated with viminol and one with pentazocine (20).

**Risk of bias**

The studies showed a high risk of bias. Figures 2 and 3 show that all studies had a high rate of bias for domain D5 (selection of the reported result). Regarding domain D4 (measurement of the outcome), 83.3 % of the studies also showed a high rate of bias. For crossover studies, domains D1 (randomization process) and DS (bias arising from period and carryover effects) presented some concerns, except for the study by Capretti and Frigerio, 1970 (19). Parallel studies presented some concerns or high risk for the D1 and D2 domains, except the study by Foschi *et al*.. (1985) (17) which presented a low risk of bias for D1 and D2 and by Nobili and Bernardi (1971) (13), low risk of bias for the D1 domain.

**Certainty of evidence**

The two evaluated outcomes had very low evidence certainty in all included studies, with risk of bias, inconsistency, indirect evidence, and imprecision being evaluated, according to Supplementary Material B.

**DISCUSSION**

The present systematic review indicates that the current available literature lacks solid evidence on efficacy and safety of viminol for pain treatment. The studies found were old and with unclear and insufficient description of their methods and results, which generates uncertainty in clinical decision-making.

The included studies showed that viminol was used for various clinical indications, such as postpartum, postoperative, and rheumatological and infectious diseases, among others. In this context, there are several indications for this drug that still need to be evaluated, within controlled clinical trials, under the scientific rigor of current clinical research, allowing the results found to be generalized to a wide range of patients (26). In addition, most of the evidence for viminol is based on studies using a single dose with a punctual evaluation, which compromises the quality of this evidence, since, according to Kostis *et al*.. (2020) (27) the ideal

duration of randomized clinical and controlled trials must be between three and five years, depending on the pathology, ensuring the reliability of the findings. Chronic pain requires long-term drug administration, thus adequate duration of these trials is essential to consolidate pharmacovigilance tools towards drug safety (28).

Regarding efficacy, there is limited evidence of the superiority of viminol over opioids. The most recent studies involving the comparison between viminol and codeine date from the 1970s. Studies showed that there were no significant differences in effect between viminol and codeine (15). Martinetti *et al*.. (1970) observed that codeine and viminol were more effective than placebo, with lesser effectiveness for viminol when administered once a day. When administered three times a day, there was no difference between viminol and codeine in the total pain intensity scores (12). In one study, pentazocine was more effective than viminol in reducing severe postpartum pain (20), while in other studies no significant difference was found between the effectiveness of viminol and pentazocine (16,17). Frigerio (1974) observed that viminol and propoxyphene were more effective than placebo, with viminol being more often effective than propoxyphene (11). Viminol was also compared with non-opioid drugs. There were no significant differences in effectiveness of aminopyrine or viminol in severe pain treatment (16). Viminol by rectal route of administration was less effective than dipyrone in severe postpartum pain (22). Comparing to benzodiazepines, viminol was more effective than chlordiazepoxide (21).

Focusing on safety, most studies involving viminol did not show adverse drug reactions (ADRs) (13,15,16,18,22,24,25). Others, in turn, reported the incidence of ADRs without clinical significance (17,23) and/or with tolerability compatible with placebo (12). Among the ADRs associated with viminol included: drowsiness and feeling hot (20,21), gastric disturbances (19), nausea, vomiting and vertigo (11). Viminol has few reports of adverse reactions in the ANVISA system (VIGIMED®). From the beginning of its VIGIMED®

computerized system (January 2018) until its last update (April 2023), only four adverse reactions were reported, being related to psychiatric disorders (asthenia, fatigue), gastrointestinal (nausea) and skin tissue disorders (pruritus). The low evidence of the safety of this medication may be related to the underreporting of adverse events, but also the lack of recent, quality studies that evaluate its adverse effects.

It should be noted that most studies that were included in this systematic review had the participation/partnership of the pharmaceutical industry (Zambon) (11–13,15–17,19,21). This is considered a concern, as biases may arise that impact the evaluation of results, study designs, reports, and inadequate conclusions as stated by some authors (29,30).

Furthermore, it should be considered that the risk of bias in all included studies was high, which implies the need to infer that the results presented in the included primary studies are subject to a greater chance of error in the estimation of the effect. Thus, the risk of bias and the uncertainty of the evidence generated by the available studies do not support the inclusion of viminol in the lists of essential medicines or its safe choice over other analgesics with more reports in the literature and greater experience of use (31–33).

Due to the existence of methodological and clinical heterogeneity, it was not possible to perform a meta-analysis. There were differences in the designs of studies with absence and/or restriction of information on randomization, blinding, and secrecy of allocation. Additionally, there are differences in participant characteristics such as diagnoses and inclusion/exclusion criteria. Thus, recognizing heterogeneity, identifying interferences in the effect measures is essential to define the beneficiary population or not of a given intervention (34)

## METHODS

This systematic review of randomized clinical trials (RCTs) was performed according to the PRISMA 2020 Statement (35) guidelines and submitted to the International Prospective Registry of Systematic Reviews (PROSPERO) under protocol number CRD42022359781. This

review addresses the following question: “Is viminol more effective and safer than other analgesics in the treatment of acute or chronic pain?”.

**Eligibility criteria**

RCTs performed with adult and elderly patients, without restriction of gender and ethnicity, who received viminol to treat acute or chronic pain were included in this review. Studies which involved children, pregnant women, or patients with hepatic or renal failure were excluded.

**Information sources**

The following databases were consulted: PubMed, EMBASE, Web of Science, Scopus, Lilacs, and Cinhal. A manual search was also performed in the gray literature (MedRxiv and BioRxiv) and in the reference list of studies retrieved from the database search. Canto *et al*.. (2020) suggest that manual searches should also involve consulting experts on the topic (33), however, this was not possible even when searching for authors in the Scopus database using the descriptor “viminol” due to the age of the articles identified (there was no contact address for the corresponding author).

**Search strategy**

The search was structured using the PICOS strategy (36) consisting of: Population (P): adults and elderly people with acute or chronic pain; Intervention (I): viminol in any route of administration and pharmaceutical form; Comparison (C): COX inhibitors and/or opioid analgesics; Outcomes (O): effectiveness and safety; and Studies (S): RCTs. In this search, no filters were used. The MesH, DeCS and Emtree descriptors were combined using the Boolean

operators “AND” and “OR”. The same search strategy was used in all databases, being adapted according to their peculiarities, when necessary (Supplementary Material A).

**Selection process**

The studies retrieved were exported to EndNote® (online version) and to Rayyan® (37). After excluding the duplicates in both software, two researchers (D.A.F.O.M. and J.M.R.) read the titles and abstracts and screened the articles that met the inclusion criteria. Subsequently, the selected studies were read in full, verifying their eligibility. In case of disagreement between them, a third researcher was consulted (R.R.R.). The agreement between researchers in the selection process was calculated by Kappa index (38), in which a result above 0.60 was considered acceptable (39)

**Data collection process**

Data extraction was performed by the same researchers independently, considering: I - General characteristics: study design, total of participants randomized and included in the study, withdrawal of participants, age, sex, degree of pain, and disease or related procedure; II - Treatment characteristics: number of participants, drug, dose, route of administration, daily doses and frequency of administration, and treatment period; and III - Outcome characteristics: treatment effectiveness and safety.

**Study risk-of-bias assessment**

The RoB 2 tool (Cochrane risk of bias for randomized studies) (40) was used for crossover and parallel trials. The analysis was also performed independently by the two researchers (D.A.F.O.M. and J.M.R.).

### Certainty of evidence

Certainty of evidence was assessed via Grading of Recommendations, Assessment, Development and Evaluation. The GRADE pro system was used employing the two outcomes (effectiveness and safety).

## LIMITATIONS

Difficulty accessing manuscripts and the not possible help of specialists due to the date of studies. The studies showed a lack of standardization of measurement instruments and many data were illegible. Furthermore, most studies have not yet accurately detailed the adverse effects reported by patients and the incidence of each of them.

## FUTURE IMPLICATIONS

Viminol lacks pharmacological studies, especially recent ones. Therefore, there is a need for a detailed investigation of this medication, supporting the search for effective alternatives to solve problems linked to pain therapy**.**

## CONCLUSION

Although viminol is approved for use by some regulatory agencies, studies on its use in pain have been found to be old, lack methodological rigor, have a high risk of bias, and low quality of evidence. Thus, although viminol appears to be effective and safe in the management of pain, the low quality of the reports generates uncertainty in clinical decision-making.

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**Table 1.** Main characteristics of the included studies.

| Authors and year (Country) | Study design | Total of Participants Randomized/included in study. (Control)/(Intervention) | Age Mean (SD) Control/ Intervention | N (%) Sex Female Control/Intervention Male Control/Intervention | Degree of pain | Disease or related procedure |
|---|---|---|---|---|---|---|
| Albernaz *et al*.., 1975 (Brazil) | Randomized Double-blind | 60/54/ (27)/ (27) | NR | NR | NR | Cervical syndromes of different etiologies, with vestibular and cochlear repercussions, Barré-Lieou Syndrome (36), vertebrobasilar insufficiency syndrome (14), Whiplash Syndrome (4) |
| Belda and Margarido, 1977 (Brazil) | Randomized | 42/42/ (10/32) | NR/50.31(NR) | NR | NR | Leprosy |
| Capretti and Frigerio, 1970 (Italy) | Randomized Double-blind Crossover | 18/18/ (18)/(18) | NR | NR | At least moderate | Pain associated with various neoplasms |
| Cinelli *et al*.., 1986 (Italy) | Randomized Double-blind | 45/42/ (28)/(14) | 48.1 (4.2) and 44.1 (4.1)/44.9 (3.8) | 12 (42.86) and 8 (28.57)/8 (28.57)<br><br>2 (14.28) and 6 (42.86)/6 (42.86) | Moderate to severe | Postoperative pain: cholecystectomy, vagotomy + pyloroplasty, gastroduodenostomy, gastrojejunostomy |
| Frigerio *et al*.., 1974 (Italy) | Randomized Double-blind Multi-centric | 1731/1731/ (1141)/(590) | NR | 329 (33.03) and 341 (34.24)/326 (32.73)<br><br>243 (33.06) and 228 (31.02)/ 264 (35.92) | Persistent painful symptoms at least 2-3 days: Moderate Strong Severe | Neurotic, osteoarticular, peripheral vascular, neoplastic, traumatic, dental, visceral origin. |
| Foschi., Ventresca and Lodola, 1985 (Italy) | Randomized Double blind | 60/60 (30)/(30) | 50.1 (4.8) and 49.6 (3.7)/54.6 (4.0) and 54.2 (3.8) | 8 (28.57) and 10 (35.71)/6 (21.43) and 4 (14.28)<br><br>5 (15.62) and 7 (21.87)/9 (28.12) and 11 (34.37) | At least moderate to severe | Abdominal surgery (postoperative pain): cholecystectomy (33), gastrectomy (8), hemicolectomy (4) and others (15) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hennay *et al*.., 1977 (Italy) | Randomized Double-blind | 49 (NR)/(NR) | NR | NR/NR | Intense | Postpartum pain and episiotomy |
| Martinetti *et al*.., 1970 (Italy) | Randomized Double-blind Crossover | Series I: 44/44/ (44)/(44) Series II: 60/60 (60)/(60) | Series I: 62(NR) Series II: 55.8(NR) | Series I: 28 (63.63) and 28 (63.63)/28 (63.63) 16 (36.36) and 16 (36.36)/ 16 (36.36) Series II: 49 (81.60) and 49 (81.60)/ 49 (81.60) 11 (18.30) and 11 (18.30)/11 (18.30) | Persist for the duration of the study. Sufficient severity to require analgesics. | Series I and II: Patients with chronic pain Series I: Single dose Skeletal and articular (10), neural (9), visceral (14), neoplastic (5) and obstructive arterial disorders (3), and headache (3) Series II: Repeated dose Chronic skeletal (bone) and articular pain (26), visceral (9), neoplastic (18) and obstructive arterial disorders (3), and headache (4) |
| Moroni, Cavalli and Lodola, 1978 (Italy) | Randomized Double-blind Crossover | 41/41/ (41)/(41) | 65.5 (NR) | 19 (46.34)/19 (46.34) and 19 (46.34) 22 (53.65)/ 22 (53.65) and 22 (53.65) | At least moderate | Chronic pain due to neoplasm (37), rheumatoid arthritis (2), coxitis (1), and lower limbartheriosclerosis obliterans (1) |
| Nobili and Bernardi, 1971 (Italy) | Randomized Double-blind | 93/93 (63)/(30) | 29.7 (0.78) and 29.8 (1.05)/30.9 (0.72) | NR/NR | Moderate Severe | Postpartum pain |
| Porsio and Borgia, 1971 (Italy) | Randomized Double-blind Crossover | 6/6 (6)/(6) | 20.67(NR)/ 20.67(NR) | NR | NR | Tuberculosis |
| Procacci *et al*.., 1969 (Italy) | Experiment 1: Randomized Double-blind Crossover Experiment 2: Randomized Double-blind Crossover | Experiment 1: 10/10 (10)/(10) Experiment 2: 30/28 (28)/(28) | Experiment 1: 20-36[a] (NR) Experiment 2: 29-74[a] (NR) | Experiment 1: NR Experiment 2: 28 males | Experiment 1: Healthy individuals Experiment 2: Severity enough to require analgesics | Experiment 1: Healthy individuals Experiment 2: Osteoarthritis, alterations low back (24), and cervical (4) |
| Signorelli and Rella, 1972 (Italy) | Randomized Double-blind | 57/57 (19)/(19) | 26.58 (NR) and 27.79 (NR)/ 27.53 (NR) | NR/NR | Severe | Postpartum pain |

| | | | | | | |
|---|---|---|---|---|---|---|
| Spilborghs, 1977 (Brazil) | Randomized, Double-blind Crossover | 20/20/ (20)/(20) | 48.1 (NR)/48.1 (NR) | 13 (NR)/13 (NR) 7 (NR)/7(NR) | NR | Chronic spinal pain in the different segments of the spine: neck pain (3), cervic-brachialgia (2), back pain (7), backache (9), lumbo-sciatica (5), trigeminal neuralgia (1) |

N: number of participants. SD: standard deviation. NR: not reported.
[a]: age range of participants

**Table 2**. Treatment characteristics: number of participants, viminol formulation, route of administration, daily doses and frequency of administration, and treatment period.

| Authors, year | N of participants who completed study (Control)/ (Intervention) | Drug (dose) Control/ Intervention | Route of administration Control/ Intervention | Daily dose Control/ Intervention | Daily frequency of administration (Control)/ (Intervention) | Treatment period |
|---|---|---|---|---|---|---|
| Albernaz *et al*.., 1975 | 54 (27/27) | Placebo/viminol (70 mg) | (oral/oral) | Placebo/240 mg | Every 8 hr | 40 days |
| Belda and Margarido, 1977 | 42 (10/32) | Thalidomide (NR)/ viminol (NR) | (oral/oral) | NR | 3 times/day | For 3 to 4 weeks |
| Capretti and Frigerio, 1970 | 18 (crossover) | Placebo and codeine (30 and 60 mg)/viminol (50 and 100 mg) | (oral/oral) | 120 mg and 240 mg / 200 mg and 400 mg | Every 4 hr | 5 days |
| Cinelli *et al*.., 1986 | 42 (14 and 14/14) | Placebo and pentazocine (30 mg)/viminol (10 mg) | (intravenous/intravenous) | 30 mg/10 mg | Single dose, 3-4 hr after operation | 1 day |
| Frigerio *et al*.., 1974 | 1731 (572 and 569/590) | Placebo and propoxyphene (65 mg)/viminol (70 mg) | (oral/oral) | 260 mg/280 mg | 4 times/day (7-8/11-12/16-18/20-22 hr) | 1 day |
| Foschi, Ventresca and Lodola, 1985 | 60 (15 and 15)/(15 and 15) | Placebo and pentazocine (30 mg)/ viminol (2.5 mg) and viminol (5 mg) | (intravenous/intravenous) | 30 mg/2.5 mg and 5.0 mg | Single dose, 3-4 hr after surgery | 1 day |
| Hennay *et al*.., 1977 | 49 (NR/NR) | Pentazocine (50 mg)/ viminol (50 mg) | (oral/oral) | 100 mg/100 mg | Single dose | 1 day |
| Martinetti *et al*.., 1970 | Series I: 44 (crossover) Series II: 60 (crossover) | Placebo and codeine (30 mg)/viminol (30 mg) | (oral and oral) | Series I: 60 mg/60 mg<br>Series II: 180 mg/180 mg | Series I: Single dose<br>Series II: 3 times/day | Series I: 1 day<br>Series II: 3 days, not consecutive |
| Moroni, Cavalli and Lodola, 1978 | 39 (crossover) | Chlordiazepoxide (10 mg)/viminol (70 mg) and viminol (70 mg) + chlordiazepoxide (10 mg) | (oral/oral) | 10 mg/70 mg and 70 mg + 10 mg | Single dose | 1 day |

| | | | | | | |
|---|---|---|---|---|---|---|
| Nobili and Bernardi, 1971 | 93 (32 and 31/30) | Placebo and codeine (60 mg) /viminol (100 mg) | (oral/oral) | 60 mg/100 mg | Single dose | 1 day |
| Porsio and Borgia, 1971 | 6 (crossover) | Placebo/viminol (50 mg) | (oral/oral) | Placebo/150 mg | 3 times/day | 30 days |
| Procacci *et al*.., 1969 | Experiment 1: 10 (crossover) Experiment 2: 28 (crossover) | Experiment 1: Codeine (60 mg) and aminopirine (2 g)/viminol (100 mg) Experiment 2: Codeine (30 mg)/viminol (50 mg) | (oral/oral) | Experiment 1: 60 mg and 2 g/100 mg Experiment 2: 120 mg/200 mg | Experiment 1: Single dose Experiment 2: 4 times/day (8 am, 12 am, 4 pm, 8 pm) | Experiment1: 1 day Experiment 2: 4 consecutive days |
| Signorelli and Rella, 1972 | 57 (19 and 19/19) | Placebo and dipyrone (1 g)/viminol (100 mg) | (rectal/rectal) | 1 g/100 mg | 12-72 hr after partum | 1 day |
| Spilborghs, 1977 | 20 (crossover) | Placebo/viminol (50 mg) | (oral/oral) | Placebo/150 mg | 3 times/day | 10 days |

N: absolute number of participants. SD: standard deviation. NR: not reported. hr: hours.

**Table 3.** Outcome characteristics: treatment effectiveness and safety.

| Authors, year | Effectiveness | | | Safety | |
|---|---|---|---|---|---|
| | **Time points measured / instrument** | **Pain scores before treatment Mean (SD) Control/Intervention** | **Pain scores after treatment Mean (SD) Control/Intervention** | **Time points measured / instrument** | **Adverse effects Mean (SD) or (*N*) Control/Intervention** |
| Albernaz *et al*.., 1975 | After treatment / qualitative analysis -improved or not improved | NR | Improved: 6 (NR)/19 (NR)<br>Not Improved: 21(NR)/8 (NR) | NR | NR |
| Belda and Margarido, 1977 | After treatment / qualitative analysis -improved or not improved | NR | Improved: 30 (NR)/2 (NR)<br>Not Improved: 2 (NR)/8 (NR) | Weekly evaluation and one week after suspension of treatment/ biochemical and urine tests | No significant changes in liver, kidney, and hematopoietic system function with viminol |
| Capretti and Frigerio, 1970 | After treatment / qualitative analysis -improved or not improved | Illegible | Illegible | At the time of the first administration and the next morning/ qualitative analysis | Low doses of viminol had placebo-like undesirable effects and gastric disturbances associated with higher doses of viminol. |
| Cinelli *et al*.., 1986 | After treatment / semi-quantitative analysis numerical rating scale | 2.14 (0.1) and 2.6 (0.1)/ 2.57 (0.1) | 6.5[b] (NR) and 12.3 (NR)/ 11.9 (NR) | After 15, 30, 45, 60 and 120 minutes/ qualitative analysis | NR |
| Foschi, Ventresca and Lodola, 1985 | After treatment / semi-quantitative analysis numerical rating scale | 2.8 (0.1) and 2.73 (0.1)/2.6 (0.1) and 2.9 (0.1) | 2.20[b] (NR) and 9.47(NR)/6.27(NR) and 9.47 (NR) | At least three observation times/ qualitative analysis | Nausea (1), sweating (1), drowsiness (3), grogginess (2), dry mouth (3), nervousness (3), dizziness (1)/ Drowsiness (1), dry mouth (1and 1), nervousness (1), sweating (1), nausea (1), head falling forward (1) |

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|---|---|---|---|---|---|
| Frigerio *et al*.., 1974 | After treatment / semi-quantitative analysis pain remission scale | NR | Pain notable: 306[c] (NR) and 349 (NR)/365(NR)<br><br>Severe pain: 71(NR) and 64(NR)/77(NR) | NR | Nausea/vomiting (18 and 24/25), drowsiness (11 and 20/9), vertigo (2 and 18/14), asthenia (6 and 5/8), headache (2 and 6/2), sweating (3 and 3/3), feeling hot (2 and 1/2), diarrhea (2 and 0/1), euphoria (and 0/1), arrhythmia (0 and 0/1), lightheadedness (4 and 5/3), allergic reaction (0 and 0/1) |
| Hennay *et al*.., 1977 | After treatment / qualitative analysis -improved or not improved | NR | Improved: 33 (NR)/26 (NR)<br><br>Not Improved: 4 (NR)/11 (NR) | For a period of two hours after using the pain reliever/ qualitative analysis | Somnolence (1/2) heat sensation (0/1) vomiting (1/0) dizziness (1/0) |
| Martinetti *et al*.., 1970 | After treatment / semi-quantitative analysis numerical rating scale | Series I and II 3.0 (NR) and 3.0 (NR)/3.0 (NR) | Series I: 3.59[b] (0.53) and 11.24 (0.53)/ 7.98 (0.67)<br><br>Series II: 5.39[d] (0.44) and 4.11(0.43)/ 3.30 (0.43) | Series I: Every hour up to 5 hours / qualitative analysis<br><br>Series II: Two hours after each dose until the next morning / qualitative analysis. | Series I: Heartburn (2), Sedation (1), Feels warm (1) and Heartburn (1), Sedation (2), Feels warm (2) / Heartburn (2) Vomiting (1), Sedation (1), Feels warm (3), Dizziness (1)<br><br>Series II: Nausea (1), Vomiting (2), Sedation (2) and Heartburn (1), Nausea (8), Vomiting (10), Sedation (2) / Heartburn (1), Nausea (2), Vomiting (6) |
| Moroni, Cavalli and Lodola, 1978 | After treatment / semi-quantitative analysis numerical rating scale | 2.73 (NR)/2.73 (NR) and 2.72 (NR) | After 1 hr: 1.23[e] (0.13)/1.70 (0.11) and 1.63(0.11)<br><br>After 2 hr: 1.17[e] (0.18)/1.53 (0.14) and 1.70 (0.12) | Before and after 1 hr and after 2 hr of treatment/ qualitative analysis | Drowsiness (NR/1/1) |

| | | | | | |
|---|---|---|---|---|---|
| Nobili and Bernardi, 1971 | After treatment / semi-quantitative analysis pain remission scale | NR | 0.94 (0.17) and 1.94 (0.16)/2.27(0.15) | After 1, 2, 3 and 4 hours/ qualitative analysis. | 0 and 0/0 |
| Porsio and Borgia, 1971 | After treatment / qualitative analysis | NR | NR | Baseline laboratory studies were repeated twice before initiating the treatment and then repeated at 10-day intervals during treatment/ qualitative and quantitative analysis | 0/0 |
| Procacci *et al*.., 1969 | After treatment / semi-quantitative analysis numerical rating scale | Experiment 1: 783.31[f] (35.2) and 803.72 (27.9)/771.20 (26.8)<br><br>Experiment 2: NR | Experiment 1:<br>872.94 [f] (31.6) and 848.55(27.3)/864.71(22.7)<br><br>Experiment 2:<br>Pain intensity<br>Cycle 1:<br>Day1:2.32(NR)/2.63(NR)<br>Day2:1.82(NR)/2.30(NR)<br>Day3:1.57(NR)/1.86(NR)<br>Day4:1.09(NR)/1.84(NR)<br>Cycle 2:<br>Day1:2.32(NR)/2.02(NR)<br>Day2:2.07(NR)/1.86(NR)<br>Day3:1.96(NR)/1.59(NR)<br>Day4:1.86(NR)/1.59(NR)<br><br>Pain alleviation:<br>Day1:1.14(NR)/1.10(NR)<br>Day2:1.17(NR)/1.17(NR)<br>Day3:1.17(NR)/1.14(NR)<br>Day 4:1.25(NR)/1.0(NR) | Experiment 1:<br>After 1 hour of administration of every formulation/ qualitative analysis<br><br>Experiment 2:<br>8am, 10am, 2pm. 6pm/ qualitative analysis | 0 and 0/0 |

| | | | | | |
|---|---|---|---|---|---|
| Signorelli and Rella, 1972 | After treatment / qualitative analysis - improved or not improved | 3.0 (NR) and 3.05 (NR)/3.10 (NR) | Improved: 6 (NR) and 14 (NR)/12 (NR)<br><br>Not Improved: 13 (NR) and 5 (NR)/7 (NR) | Every 2 hours after treatment/ qualitative analysis | 0 and 0/0 |
| Spilborghs, 1977 | After treatment / qualitative analysis -improved or not improved | NR | Improved: 7 (NR)/19 (NR)<br><br>Not Improved: 13 (NR)/1 (NR) | After 10 days/ qualitative analysis | A single patient, at the beginning of treatment with viminol, reported mild dizziness that disappeared without the need to suspend treatment. |

VAS: visual analogue scale. SD: standard deviation. N: absolute number of participants. NR: not reported. VRS: verbal rating scale. hr: hours. CI: confidence interval. NS: not significant.

[b:] Sum of total pain relief – data inversely proportional to pain

[c]: Positive effect on pain: Number of patients with pain remission for lower scores

[d]: Total daily pain intensity

[e]: Analgesia score

[f]: Pain threshold measurement

## Figures

**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Page *et al*.., 2020).

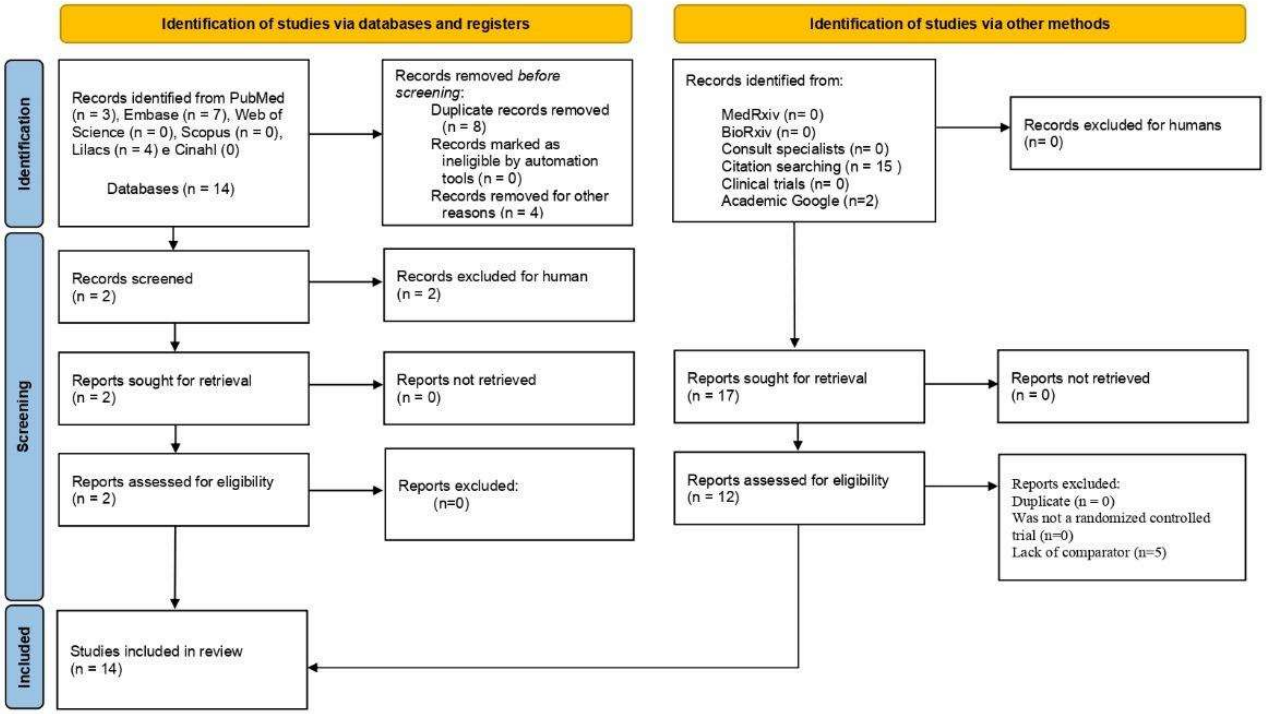
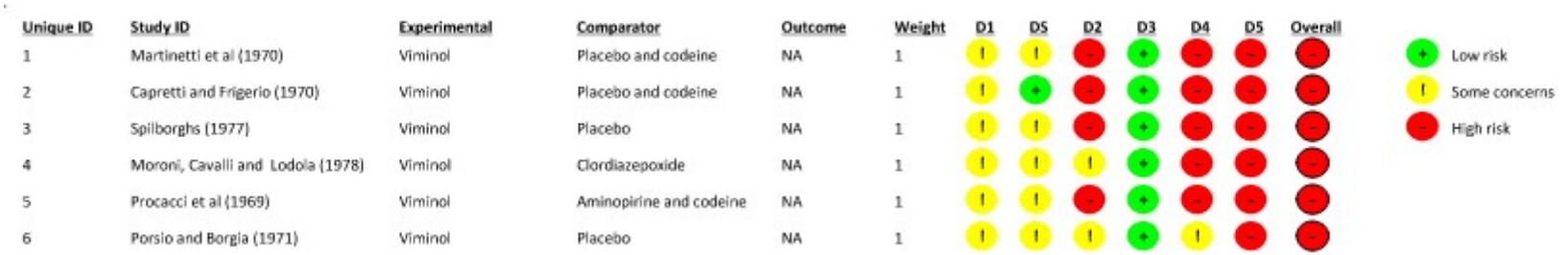
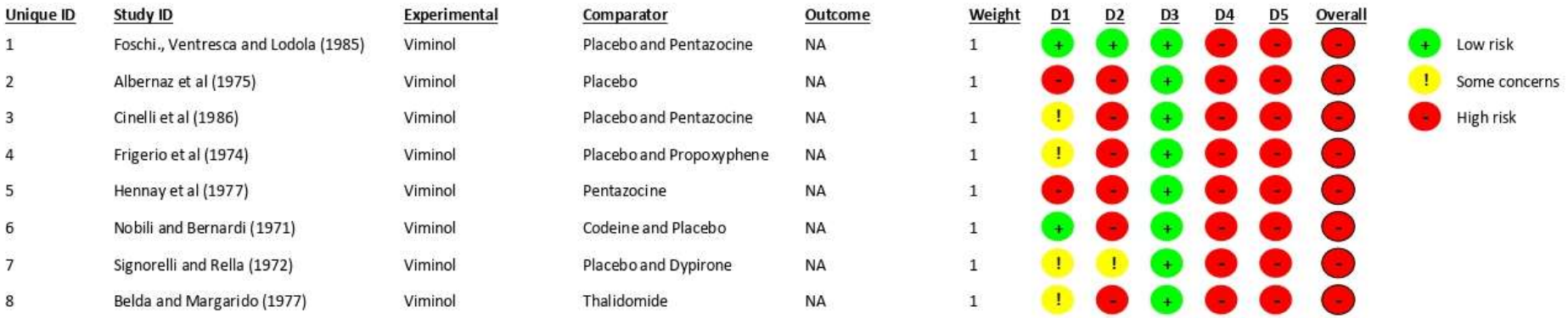


**Figure 2.** Risk of bias in crossover studies.




Abbreviations - D1: Randomization process; D2: Deviations from the intended interventions; D3: Missing outcome data; D4: Measurement of the outcome; D5: Selection of the reported result.

**Figure 3.** Risk of bias in parallel studies.




Abbreviations - D1: Randomization process; D2: Deviations from the intended interventions; D3: Missing outcome data; D4: Measurement of the outcome; D5: Selection of the reported result.

## Supplementary Material A. Database search strategy

| Database | | Search strategy | N |
|---|---|---|---|
| **PUBMED** (31/07/2024) | #1 | ("Patients"[Mesh]) OR (Patient) OR (Clients) OR (Client) OR ("Acute Pain"[Mesh]) OR (Acute Pains) OR ("Chronic Pain"[Mesh]) OR (Chronic Pains) OR (Widespread Chronic Pain) OR (Widespread Chronic Pains) OR ("Pain, Postoperative"[Mesh]) OR (Post-surgical Pain) OR (Post surgical Pain) OR (Postoperative Pain) OR (Postsurgical Pain) OR (Post-operative Pain) OR (Post operative Pain) OR (Post-operative Pains) OR (Chronic Postsurgical Pain) OR (Chronic Postsurgical Pains) OR (Persistent Postsurgical Pain) OR (Chronic Postoperative Pain) OR (Chronic Post-operative Pain) OR (Chronic Post operative Pain) OR (Chronic Post-surgical Pain) OR (Chronic Post surgical Pain) OR (Acute Postoperative Pain) OR (Acute Post-operative Pain) OR (Acute Post operative Pain) | |
| | #2 | ("viminol" [Supplementary Concept]) OR (diviminol) OR (1-(1-(2-chlorobenzyl)-2-pyrrolyl)-2-(di-sec-butylamino)ethanol) OR (Z 424) OR (Z-424) OR ("dividol" [Supplementary Concept]) OR (viminol p-hydroxybenzoate) OR (viminol para-hydroxybenzoate) OR (viminol 4-hydroxybenzoate) OR (viminol 4-hydroxybenzoate, viminol 4-hydroxybenzoate (1:1)) | |
| | #3 | ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh]) OR (NSAID) OR (Nonsteroidal Anti-Inflammatory Agent) OR (Nonsteroidal Anti Inflammatory Agent) OR (NSAIDs) OR (Nonsteroidal Antiinflammatory Agents) OR (Non-Steroidal Anti-Inflammatory Agents) OR (Non Steroidal Anti Inflammatory Agents) OR (Nonsteroidal Anti-Inflammatory Agents) OR (Nonsteroidal Anti Inflammatory Agents) OR (Non-Steroidal Anti-Inflammatory Agent) OR (Anti-Inflammatory Analgesics) OR (Aspirin-Like Agents) OR (Aspirin Like Agents) OR (Aspirin-Like Agent) OR (Aspirin Like Agent) OR ("Dipyrone"[Mesh]) OR (Methamizole) OR (Metamizol) OR (Dipyronium) OR (Metamizole) OR (Biopyrin) OR (Novalgetol) OR (Novalgin) OR (Pyralgin) OR (Novaminsulfone) OR (Sulpyrin) OR (Sulpyrine) OR (Optalgin) OR (Noramidopyrine Methanesulfonate Sodium) OR (Novamidazophen) OR (Metamizole Sodium) OR (Methampyrone) OR (Algopyrin) OR (Analgin) OR (Narone) OR (Noramidopyrine Methanesulfonate) OR (Normelubrine) OR ("Acetaminophen"[Mesh]) OR (Acetominophen) OR (Hydroxyacetanilide) OR (APAP) OR (p-Acetamidophenol) OR (p-Hydroxyacetanilide) OR (Paracetamol) OR (N-(4-Hydroxyphenyl)acetanilide) OR (Acetamidophenol) OR (N-Acetyl-p-aminophenol) OR (Acephen) OR (Acetaco) OR (Tylenol) OR (Anacin-3) OR (Anacin 3) OR (Anacin3) OR (Datril) OR (Panadol) OR (Acamol) OR (Algotropyl) OR ("Analgesics, Opioid"[Mesh]) OR (Opioid Analgesics) OR (Opioid Analgesic) OR (Opioids) OR (Opioid) OR (Partial Opioid Agonists) OR (Opioid Partial Agonists) OR (Full Opioid Agonists) OR (Opioid Full Agonists) OR (Opioid Mixed Agonist-Antagonists) | |

| | | | |
|---|---|---|---|
| | (#1) AND (#2) AND (#3) | | 3 |
| **LILACS** (31/07/2024) | #1 | ("Patients") OR ("Pacientes") OR (Patient) OR (Clients) OR (Client) OR ("Acute Pain") OR (" Dor aguda" ) OR (Acute Pains) OR ("Dolor agudo") OR ("Chronic Pain") OR ("Dor crônica") OR ("Dolor crônico") OR (Chronic Pains) OR (Widespread Chronic Pain) OR (Widespread Chronic Pains) OR ("Pain, Postoperative") OR (Post-surgical Pain) OR (Post surgical Pain) OR (Postoperative Pain) OR (Postsurgical Pain) OR (Post-operative Pain) OR (Post operative Pain) OR (Post-operative Pains) OR (Chronic Postsurgical Pain) OR (Chronic Postsurgical Pains) OR (Persistent Postsurgical Pain) OR (Chronic Postoperative Pain) OR (Chronic Post-operative Pain) OR (Chronic Post operative Pain) OR (Chronic Post-surgical Pain) OR (Chronic Post surgical Pain) OR (Acute Postoperative Pain) OR (Acute Post-operative Pain) OR (Acute Post operative Pain) | |
| | #2 | (viminol) OR (diviminol) OR ("1-1-2-chlorobenzyl-2-pyrrolyl-2-di-sec-butylaminoethanol") OR (Z424) OR (Z-424) OR (dividol) OR ("viminol p-hydroxybenzoate") OR ("viminol para-hydroxybenzoate") OR ("viminol 4-hydroxybenzoate") OR ("viminol 4-hydroxybenzoate, viminol 4-hydroxybenzoate 1:1") | |
| | #3 | ("Anti-Inflammatory Agents, Non-Steroidal") OR (NSAID) OR (Nonsteroidal Anti-Inflammatory Agent) OR (Nonsteroidal Anti Inflammatory Agent) OR (NSAIDs) OR (Nonsteroidal Antiinflammatory Agents) OR (Non-Steroidal Anti-Inflammatory Agents) OR (Non Steroidal Anti Inflammatory Agents) OR (Nonsteroidal Anti-Inflammatory Agents) OR (Nonsteroidal Anti Inflammatory Agents) OR (Non-Steroidal Anti-Inflammatory Agent) OR (Anti-Inflammatory Analgesics) OR ("Anti-Inflammatory Agents, Non-Steroidal") OR (NSAID) OR (Nonsteroidal Anti-Inflammatory Agent) OR (Nonsteroidal Anti Inflammatory Agent) OR (NSAIDs) OR (Nonsteroidal Antiinflammatory Agents) OR (Non-Steroidal Anti-Inflammatory Agents) OR (Non Steroidal Anti Inflammatory Agents) OR (Nonsteroidal Anti-Inflammatory Agents) OR (Nonsteroidal Anti Inflammatory Agents) OR (Non-Steroidal Anti-Inflammatory Agent) OR ("Anti-Inflamatórios") OR ("Antiinflamatorios") OR (Anti-Inflammatory Analgesics) OR (Aspirin-Like Agents) OR (Aspirin Like Agents) OR (Aspirin-Like Agent) OR (Aspirin Like Agent) OR ("Dipyrone") OR (Methamizole) OR (Metamizol) OR (Dipyronium) OR (Metamizole) OR (Biopyrin) OR (Novalgetol) OR (Novalgin) OR (Pyralgin) OR (Novaminsulfone) OR (Sulpyrin) OR (Sulpyrine) OR (Optalgin) OR (Noramidopyrine Methanesulfonate Sodium) OR (Novamidazophen) OR (Metamizole Sodium) OR (Methampyrone) OR (Algopyrin) OR (Analgin) OR (Narone) OR (Noramidopyrine Methanesulfonate) OR (Normelubrine) OR ("Acetaminofen") OR ("Acetaminofén") OR ("Acetaminophen") OR (Acetominophen) OR (Hydroxyacetanilide) OR (APAP) OR (p-Acetamidophenol) OR (p-Hydroxyacetanilide) OR (Paracetamol) OR (N-(4-Hydroxyphenyl)acetanilide) OR | |

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| | | (Acetamidophenol) OR (N-Acetyl-p-aminophenol) OR (Acephen) OR (Acetaco) OR (Tylenol) OR (Anacin-3) OR (Anacin 3) OR (Anacin3) OR (Datril) OR (Panadol) OR (Acamol) OR (Algotropyl) OR ("Analgesics, Opioid") OR (Opioid Analgesics) OR (Opioid Analgesic) OR (Opioids) OR (Opioid) OR ("Analgésicos Opioides") OR (Partial Opioid Agonists) OR (Opioid Partial Agonists) OR (Full Opioid Agonists) OR (Opioid Full Agonists) OR (Opioid Mixed Agonist-Antagonists) (Aspirin-Like Agents) OR (Aspirin Like Agents) OR (Aspirin-Like Agent) OR (Aspirin Like Agent) OR ("Dipyrone") OR (Methamizole) OR (Metamizol) OR (Dipyronium) OR (Metamizole) OR (Biopyrin) OR (Novalgetol) OR (Novalgin) OR (Pyralgin) OR (Novaminsulfone) OR (Sulpyrin) OR (Sulpyrine) OR (Optalgin) OR (Noramidopyrine Methanesulfonate Sodium) OR (Novamidazophen) OR (Metamizole Sodium) OR (Methampyrone) OR (Algopyrin) OR (Analgin) OR (Narone) OR (Noramidopyrine Methanesulfonate) OR (Normelubrine) OR ("Acetaminophen") OR (Acetominophen) OR (Hydroxyacetanilide) OR (APAP) OR (p-Acetamidophenol) OR (p-Hydroxyacetanilide) OR (Paracetamol) OR (N-(4-Hydroxyphenyl)acetanilide) OR (Acetamidophenol) OR (N-Acetyl-p-aminophenol) OR (Acephen) OR (Acetaco) OR (Tylenol) OR (Anacin-3) OR (Anacin 3) OR (Anacin3) OR (Datril) OR (Panadol) OR (Acamol) OR (Algotropyl) OR ("Analgesics, Opioid") OR (Opioid Analgesics) OR (Opioid Analgesic) OR (Opioids) OR (Opioid) OR (Partial Opioid Agonists) OR (Opioid Partial Agonists) OR (Full Opioid Agonists) OR (Opioid Full Agonists) OR (Opioid Mixed Agonist-Antagonists) | |
| | (#1) AND (#2) AND (#3) | | 4 |
| **WEB OF SCIENCE** (31/07/2024) | #1 | ("Patients") OR (Patient) OR (Clients) OR (Client) OR ("Acute Pain") OR (Acute Pains) OR ("Chronic Pain") OR (Chronic Pains) OR (Widespread Chronic Pain) OR (Widespread Chronic Pains) OR ("Pain, Postoperative") OR (Post-surgical Pain) OR (Post surgical Pain) OR (Postoperative Pain) OR (Postsurgical Pain) OR (Post-operative Pain) OR (Post operative Pain) OR (Post-operative Pains) OR (Chronic Postsurgical Pain) OR (Chronic Postsurgical Pains) OR (Persistent Postsurgical Pain) OR (Chronic Postoperative Pain) OR (Chronic Post-operative Pain) OR (Chronic Post operative Pain) OR (Chronic Post-surgical Pain) OR (Chronic Post surgical Pain) OR (Acute Postoperative Pain) OR (Acute Post-operative Pain) OR (Acute Post operative Pain) | |
| | #2 | ("viminol" [Supplementary Concept]) OR (diviminol) OR (1-(1-(2-chlorobenzyl)-2-pyrrolyl)-2-(di-sec-butylamino)ethanol) OR (Z 424) OR (Z-424) OR ("dividol" [Supplementary Concept]) OR (viminol p-hydroxybenzoate) OR (viminol para-hydroxybenzoate) OR (viminol 4-hydroxybenzoate) OR (viminol 4-hydroxybenzoate, viminol 4-hydroxybenzoate (1:1)) | |
| | #3 | ("Anti-Inflammatory Agents, Non-Steroidal") OR (NSAID) OR (Nonsteroidal Anti-Inflammatory Agent) OR (Nonsteroidal Anti Inflammatory Agent) OR | |

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| | | (NSAIDs) OR (Nonsteroidal Antiinflammatory Agents) OR (Non-Steroidal Anti-Inflammatory Agents) OR (Non Steroidal Anti Inflammatory Agents) OR (Nonsteroidal Anti-Inflammatory Agents) OR (Nonsteroidal Anti Inflammatory Agents) OR (Non-Steroidal Anti-Inflammatory Agent) OR (Anti-Inflammatory Analgesics) OR (Aspirin-Like Agents) OR (Aspirin Like Agents) OR (Aspirin-Like Agent) OR (Aspirin Like Agent) OR ("Dipyrone") OR (Methamizole) OR (Metamizol) OR (Dipyronium) OR (Metamizole) OR (Biopyrin) OR (Novalgetol) OR (Novalgin) OR (Pyralgin) OR (Novaminsulfone) OR (Sulpyrin) OR (Sulpyrine) OR (Optalgin) OR (Noramidopyrine Methanesulfonate Sodium) OR (Novamidazophen) OR (Metamizole Sodium) OR (Methampyrone) OR (Algopyrin) OR (Analgin) OR (Narone) OR (Noramidopyrine Methanesulfonate) OR (Normelubrine) OR ("Acetaminophen") OR (Acetominophen) OR (Hydroxyacetanilide) OR (APAP) OR (p-Acetamidophenol) OR (p-Hydroxyacetanilide) OR (Paracetamol) OR (N-(4-Hydroxyphenyl)acetanilide) OR (Acetamidophenol) OR (N-Acetyl-p-aminophenol) OR (Acephen) OR (Acetaco) OR (Tylenol) OR (Anacin-3) OR (Anacin 3) OR (Anacin3) OR (Datril) OR (Panadol) OR (Acamol) OR (Algotropyl) OR ("Analgesics, Opioid") OR (Opioid Analgesics) OR (Opioid Analgesic) OR (Opioids) OR (Opioid) OR (Partial Opioid Agonists) OR (Opioid Partial Agonists) OR (Full Opioid Agonists) OR (Opioid Full Agonists) OR (Opioid Mixed Agonist-Antagonists) | |
| | (#1) AND (#2) AND (#3) | | 0 |
| **EMBASE** (31/07/2024) | #1 | Patients OR Patient/exp OR Patient OR Clients OR Client OR 'Acute Pain' OR Pain/exp OR Pain OR 'Acute Pains' OR 'Chronic Pain'/exp OR 'Chronic Pain' OR 'Chronic Pains' OR 'Widespread Chronic Pain' OR 'Widespread Chronic Pains' OR 'Post-surgical Pain' OR 'Post surgical Pain' OR 'Postoperative Pain'/exp OR 'Postoperative Pain' OR 'Postsurgical Pain' OR 'Post-operative Pain' OR 'Post operative Pain' OR 'Post-operative Pains' OR 'Chronic Postsurgical Pain' OR 'Chronic Postsurgical Pains' OR 'Persistent Postsurgical Pain' OR 'Chronic Postoperative Pain' OR 'Chronic Post-operative Pain' OR 'Chronic Post operative Pain' OR 'Chronic Post-surgical Pain' OR 'Chronic Post surgical Pain' OR 'Acute Postoperative Pain' OR 'Acute Post-operative Pain' OR 'Acute Post operative Pain' | 1.304.427 |
| | #2 | 'viminol'/exp OR 'viminol' OR diviminol OR '1-1-2-chlorobenzyl-2-pyrrolyl-2-di-sec-butylaminoethanol' OR 'Z 424' OR 'Z-424' OR 'dividol' OR 'viminol p-hydroxybenzoate' OR 'viminol para-hydroxybenzoate' OR 'viminol 4-hydroxybenzoate'/exp OR 'viminol 4-hydroxybenzoate' OR 'viminol 4-hydroxybenzoate, viminol 4-hydroxybenzoate 1:1' | 100 |
| | #3 | 'Anti-Inflammatory Agents, Non-Steroidal' OR NSAID OR 'Nonsteroidal Anti-Inflammatory Agent' OR 'Nonsteroidal Anti Inflammatory Agent' OR NSAIDs OR 'Nonsteroidal Antiinflammatory Agents'/exp OR 'Nonsteroidal Antiinflammatory Agents' OR 'Non- | 397.972 |

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| | | Steroidal Anti-Inflammatory Agents' OR 'Non Steroidal Anti Inflammatory Agents' OR 'Nonsteroidal Anti-Inflammatory Agents' OR 'Nonsteroidal Anti Inflammatory Agents' OR 'Non-Steroidal Anti-Inflammatory Agent' OR 'Anti-Inflammatory Analgesics' OR 'Aspirin-Like Agents' OR 'Aspirin Like Agents' OR 'Aspirin-Like Agent' OR 'Aspirin Like Agent' OR Dipyrone/exp OR Dipyrone OR Methamizole OR Metamizol OR Dipyronium OR Metamizole OR Biopyrin OR Novalgetol OR Novalgin OR Pyralgin OR Novaminsulfone OR Sulpyrin OR Sulpyrine OR Optalgin OR 'Noramidopyrine Methanesulfonate Sodium' OR Novamidazophen OR 'Metamizole Sodium' OR Methampyrone OR Algopyrin OR Analgin OR Narone OR 'Noramidopyrine Methanesulfonate' OR Normelubrine OR 'Acetaminophen' OR Acetominophen OR Hydroxyacetanilide OR APAP OR 'p-Acetamidophenol' OR 'p-Hydroxyacetanilide' OR Paracetamol/exp OR Paracetamol OR 'N-4-Hydroxyphenylacetanilide' OR Acetamidophenol OR 'N-Acetyl-p-aminophenol' OR Acephen OR Acetaco OR Tylenol OR 'Anacin-3' OR 'Anacin 3' OR Anacin3 OR Datril OR Panadol OR Acamol OR Algotropyl OR 'Opioid Analgesics' OR 'Opioid Analgesic' OR Opioids OR Opioid OR Opiate/exp OR Opiate OR 'Partial Opioid Agonists' OR 'Opioid Partial Agonists' OR 'Full Opioid Agonists' OR 'Opioid Full Agonists' OR 'Opioid Mixed Agonist-Antagonists' | |
| | (#1) AND (#2) AND (#3) | | 7 |
| **SCOPUS** (31/07/2024) | #1 | Patients OR Patient OR Clients OR Client OR 'Acute Pain' OR 'Acute Pains' OR 'Chronic Pain' OR 'Chronic Pains' OR 'Widespread Chronic Pain' OR 'Widespread Chronic Pains' OR 'Post-surgical Pain' OR 'Post surgical Pain' OR 'Postoperative Pain' OR 'Postsurgical Pain' OR 'Post-operative Pain' OR 'Post operative Pain' OR 'Post-operative Pains' OR 'Chronic Postsurgical Pain' OR 'Chronic Postsurgical Pains' OR 'Persistent Postsurgical Pain' OR 'Chronic Postoperative Pain' OR 'Chronic Post-operative Pain' OR 'Chronic Post operative Pain' OR 'Chronic Post-surgical Pain' OR 'Chronic Post surgical Pain' OR 'Acute Postoperative Pain' OR 'Acute Post-operative Pain' OR 'Acute Post operative Pain' | |
| | #2 | viminol OR diviminol OR '1-1-2-chlorobenzyl-2-pyrrolyl-2-di-sec-butylaminoethanol' OR Z424 OR 'Z-424' OR dividol OR 'viminol p-hydroxybenzoate' OR 'viminol para-hydroxybenzoate' OR 'viminol 4-hydroxybenzoate' OR 'viminol 4-hydroxybenzoate, viminol 4-hydroxybenzoate 1:1' | |
| | #3 | NSAID OR 'Nonsteroidal Anti-Inflammatory Agent' OR 'Nonsteroidal Anti Inflammatory Agent' OR NSAIDs OR 'Nonsteroidal Antiinflammatory Agents' OR 'Non-Steroidal Anti-Inflammatory Agents' OR 'Non Steroidal Anti Inflammatory Agents' OR 'Nonsteroidal Anti-Inflammatory Agents' OR 'Nonsteroidal Anti Inflammatory Agents' OR 'Non-Steroidal Anti-Inflammatory Agent' OR 'Anti-Inflammatory Analgesics' OR 'Aspirin-Like Agents' OR 'Aspirin Like Agents' OR | |

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| | | 'Aspirin-Like Agent' OR 'Aspirin Like Agent' OR Dipyrone OR Methamizole OR Metamizol OR Dipyronium OR Metamizole OR Biopyrin OR Novalgetol OR Novalgin OR Pyralgin OR Novaminsulfone OR Sulpyrin OR Sulpyrine OR Optalgin OR 'Noramidopyrine Methanesulfonate Sodium' OR Novamidazophen OR 'Metamizole Sodium' OR Methampyrone OR Algopyrin OR Analgin OR Narone OR 'Noramidopyrine Methanesulfonate' OR Normelubrine OR 'Acetaminophen' OR Acetominophen OR Hydroxyacetanilide OR APAP OR 'p-Acetamidopheno' OR 'p-Hydroxyacetanilide' OR Paracetamol OR `N-4-Hydroxyphenylacetanilide` OR Acetamidophenol OR 'N-Acetyl-p-aminophenol' OR Acephen OR Acetaco OR Tylenol OR 'Anacin-3' OR 'Anacin 3' OR Anacin3 OR Datril OR Panadol OR Acamol OR Algotropyl OR 'Opioid Analgesics' OR 'Opioid Analgesic' OR Opioids OR Opioid OR 'Partial Opioid Agonists' OR 'Opioid Partial Agonists' OR 'Full Opioid Agonists' OR 'Opioid Full Agonists' OR 'Opioid Mixed Agonist-Antagonists' | |
| | (#1) AND (#2) AND (#3) | | **0** |
| **CINHAL** (31/07/2024) | #1 | ("Patients") OR (Patient) OR (Clients) OR (Client) OR MH ("Acute Pain") OR ("Acute Pain") OR ("Acute Pains") OR MH ("Chronic Pain") OR ("Chronic Pain") OR ("Chronic Pains") OR ("Widespread Chronic Pain") OR ("Widespread Chronic Pains") OR MH (Pain Postoperative) OR ("Pain Postoperative") OR ("Post-surgical Pain") OR ("Post surgical Pain") OR ("Postoperative Pain") OR ("Postsurgical Pain") OR ("Post-operative Pain") OR ("Post operative Pain") OR ("Post-operative Pains") OR ("Chronic Postsurgical Pain") OR ("Chronic Postsurgical Pains") OR ("Persistent Postsurgical Pain") OR ("Chronic Postoperative Pain") OR ("Chronic Post-operative Pain") OR ("Chronic Post operative Pain") OR ("Chronic Post-surgical Pain") OR ("Chronic Post surgical Pain") OR ("Acute Postoperative Pain") OR ("Acute Post-operative Pain") OR ("Acute Post operative Pain") | |
| | #2 | ("viminol") OR (diviminol) OR ("1-(1-(2-chlORobenzyl)-2-pyrrolyl)-2-(di-sec-butylamino)ethanol") OR (Z 424) OR (Z-424) OR ("dividol") OR ("viminol p-hydroxybenzoate") OR ("viminol para-hydroxybenzoate") OR ("viminol 4-hydroxybenzoate") OR ("viminol 4-hydroxybenzoate, viminol 4-hydroxybenzoate (1:1)") | |
| | #3 | MH ("Anti-Inflammatory Agents non-Steroidal") OR ("Anti-Inflammatory Agents non-Steroidal") OR (NSAID) OR ("Nonsteroidal Anti-Inflammatory Agent") OR ("Nonsteroidal Anti Inflammatory Agent") OR (NSAIDs) OR ("Nonsteroidal Antiinflammatory Agents") OR ("Non-Steroidal Anti-Inflammatory Agents") OR ("Non Steroidal Anti Inflammatory Agents") OR ("Nonsteroidal Anti-Inflammatory Agents") OR ("Nonsteroidal Anti Inflammatory Agents") OR ("Non-Steroidal Anti-Inflammatory Agent") OR ("Anti-Inflammatory Analgesics") OR ("Aspirin-Like Agents") OR ("Aspirin Like Agents") OR ("Aspirin-Like Agent") OR ("Aspirin Like Agent") OR ("Dipyrone") OR (Methamizole) OR (Metamizol) OR (Dipyronium) OR (Metamizole) OR | |

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| | | (Biopyrin) OR (Novalgetol) OR (Novalgin) OR (Pyralgin) OR (Novaminsulfone) OR (Sulpyrin) OR (Sulpyrine) OR (Optalgin) OR (“NORamidopyrine Methanesulfonate Sodium”) OR (Novamidazophen) OR (“Metamizole Sodium”) OR (Methampyrone) OR (Algopyrin) OR (Analgin) OR (Narone) OR (“NORamidopyrine Methanesulfonate”) OR (NORmelubrine) OR ("Acetaminophen") OR MH (“Acetaminophen”) OR (Hydroxyacetanilide) OR (APAP) OR (“p-Acetamidophenol”) OR (“p-Hydroxyacetanilide”) OR (Paracetamol) OR (“N-(4-Hydroxyphenyl)acetanilide”) OR (Acetamidophenol) OR (“N-Acetyl-p-aminophenol”) OR (Acephen) OR (Acetaco) OR (Tylenol) OR (Anacin-3) OR (Anacin 3) OR (Anacin3) OR (Datril) OR (Panadol) OR (Acamol) OR (Algotropyl) OR MH ("Analgesics, Opioid") OR (“Analgesics, Opioid”) OR (“Opioid Analgesics”) OR (“Opioid Analgesic”) OR (Opioids) OR (Opioid) OR (“Partial Opioid Agonists”) OR (“Opioid Partial Agonists”) OR (“Full Opioid Agonists”) OR (“Opioid Full Agonists”) OR (“Opioid Mixed Agonist-Antagonists”) OR MH ("Aspirin") OR ("Aspirin") OR (“Acetylsalicylic Acid”) OR (“2-(Acetyloxy)benzoic Acid”) OR (Micristin) OR (Solprin) OR (Solupsan) OR (ZORprin) OR (Acetysal) OR (Acylpyrin) OR (Aloxiprimum) OR (Colfarit) OR (Dispril) OR (Easprin) OR (Ecotrin) OR (Endosprin) OR (Magnecyl) OR (Polopirin) OR (Polopiryna) OR ("Meloxicam") OR (Miloxicam) OR (Parocin) OR (Mobic) OR (Mobicox) OR (Mobec) OR (Masflex) OR (Movicox) OR (Reumoxicam) OR (Uticox) OR (Movalis) OR ("nimesulide") OR (R-805) OR (“4-nitro-2-phenoxymethanesulfonanilide”) OR (R 805) OR (Aulin) OR (Eskaflam) OR (lizepat) OR (Mesulid) OR (Nexen) OR (Nimesil) OR (Redaflam) OR (Antifloxil) OR (Guaxan) OR MH ("Ibuprofen") OR ("Ibuprofen") OR (“alpha-Methyl-4-(2-methylpropyl)benzeneacetic Acid”) OR (Ibumetin) OR (“Ibuprofen-Zinc”) OR (Motrin) OR (Nuprin) OR (Rufen) OR (Salprofen) OR (“Trauma-Dolgit Gel”) OR (“Trauma Dolgit Gel”) OR (Brufen) OR ("Diclofenac”) OR MH ("Diclofenac”) OR (Diclophenac) OR (Dicrofenac) OR (Dichlofenal) OR (“Diclofenac Sodium”) OR (“Sodium Diclofenac”) OR (“Diclonate P”) OR (FelORan) OR (Voltarol) OR (Novapirina) OR (ORthofen) OR (ORtofen) OR (ORthophen) OR (SR-38) OR (“SR 38”) OR (SR38) OR (Voltaren) OR (“Diclofenac Potassium”) OR ("Celecoxib") OR (“4-(5-(4-methylphenyl)-3-(trifluORomethyl)-1H-pyrazol-1-yl)benzenesulfonamide”) OR (Celebrex) OR (SC 58635) OR (SC-58635) OR (SC58635) OR MH (“Cox-2 Inhibitors”) OR (“Cox-2 Inhibitors”) | |
| | (#1) AND (#2) AND (#3) | | **0** |

## Supplementary Material B. Certainty of evidence

| Certainty assessment | | | | | | | Summary of findings | | |
|---|---|---|---|---|---|---|---|---|---|
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Impact |
| | | | | | | | With analgesics opioid e nonopioids | With Viminol | |
| **Effectiveness (follow-up: range 1 days to 40 days; assessed with: pain reduction)** | | | | | | | | | |
| 0 (13 RCTs) | very serious[a] | very serious[b] | serious[c] | very serious[d] | publication bias strongly suspected[e] | ⊕◯◯◯ Very low | These are old studies, without methodological rigor, with a high risk of bias. Thus, there is a lack of studies to validate or disapprove the use of viminol in clinical practice, even replacing other analgesics.[f] | | |
| **Security (follow-up: range 1 days to 40 days; assessed with: Adverse Drug Reaction Induction)** | | | | | | | | | |
| 0 (14 RCTs) | very serious[g] | very serious[h] | serious[i] | very serious[j] | publication bias strongly suspected[k] | ⊕◯◯◯ Very low | It becomes complex to assess the certainty of the evidence of studies that show the safety of the drug in uncontrolled clinical trials, without methodological rigor and sponsored by the pharmaceutical industry. | | |

**Explanations**

a. Most studies showed a high risk of bias for D2 (Deviations from the intended interventions) in the in assessing the risk of bias. The domains D4 (Measurement of the outcome) and D5 (Selection of the reported result) in the Robin System has a high bias rating for most studies, too.

b. There is heterogeneity in the proposed methodologies for pain assessment, intervention, and control group doses, in addition to clinical heterogeneity.

c. The results of the studies have limitations for extrapolation to the general population due to the low number of participants, short-term evaluation, and non-standardization of doses in the intervention and control groups.

d. The studies involve a low number of patients and events, but the effect estimates do not show variations from large risks to benefits.

e. Due to the limited search in the literature, evidence from small studies and most of them funded by the pharmaceutical industry, there is a high publication bias.

f. These are old studies, without methodological rigor, with a high risk of bias. Thus, there is a lack of studies to validate or disapprove the use of viminol in clinical practice, even replacing other analgesics.

g. Most of the studies classified as having a high risk of bias in domains D2, D4 and D5 of the Robin System.

h. Due to the subjective method of evaluating the tolerability of the intervention and control groups, it is difficult to overlap the results.

i. The results presented cannot be extrapolated, since the number of participants is low, without considering special groups.

j. There is a narrow confidence interval, since the intervention group was tolerable to viminol, but the number of participants was very limited and without methodological rigor.

k. Evidence from small, industry-sponsored studies.

## 4 CONSIDERAÇÕES FINAIS

Com relação à implantação da FV na Santa Casa de Alfenas-MG, foi realizada a capacitação dos profissionais de saúde. Apresentando a intervenção educativa resultados satisfatórios no incremento do conhecimento em FV e estando capacitados em detectar os EAM, houve aumento no número de notificações.

No geral, os três analgésicos em estudo mostraram-se seguros, com baixa incidência de RAM. Dentre eles, o tapentadol liderou a incidência de RAM, seguido do viminol e dipirona, que se mostrou como a mais segura, visto que foi muito bem tolerada pelos pacientes, sendo o mais prescrita e utilizada. Dessa forma, a segurança da dipirona reforça a possibilidade de sua indicação clínica tanto na dor aguda, como crônica.

Sobre o viminol, seus estudos são antigos e carecem de rigor metodológico para melhorar a robustez das evidências geradas. Faltam estudos mais recentes e completos para orientar a escolha clínica do viminol na dor aguda ou crônica.

Além dos artigos apresentados, a doutoranda publicou uma revisão narrativa sobre o tapentadol (“TAPENTADOL, AN OPIOID AS A STRATEGY FOR THE TREATMENT OF CHRONIC PAIN? A NARRATIVE REVIEW") no *Journal of Pharmaceutical and Biological Sciences* e em colaboração; uma revisão sistemática sobre a dipirona (“SAFETY OF METAMIZOLE (DIPYRONE) FOR THE TREATMENT OF MILD TO MODERATE PAIN - AN OVERVIEW OF SYSTEMATIC REVIEWS”) no *Naunyn-Schmiedeberg's Archives of Pharmacology*.

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