EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 6
05-17
Year: 2021

PARACETAMOL: HOT CLINICAL QUESTIONS

Francesco Perticone[1], Gian Luigi de'Angelis[2], Loreto Gesualdo[3], Alessandra Graziottin[4], Alessandra Mangia*[5] and Stefano Vicari[6]

[1]Department of Medical and Surgical Sciences, University of Catanzaro Magna Graecia, Italy.
[2]Department of Medicine and Surgery, University of Parma, Gastroenterology and Endoscopy Unit, University Hospital of Parma, Italy. Department of Emergency and Organ Transplantation
[3]Department of Emergency and Organ Transplantation, "Aldo Moro" University, Bari, Nephrology, Dialysis and Transplantation Unit, "Policlinico" University Hospital, Bari, Italy.
[4]Center of Gynecology and Medical Sexology H. San Raffaele Resnati Milan, Italy; Graziottin Foundation for the Cure and Care of Pain in Women, NPO, Italy.
[5]Liver Unit, Medical Science Department, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo (FG), Italy.
[6]Department of Neurosciences, Child and Adolescent Neuropsychiatry Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy.

***Corresponding Author: Alessandra Mangia**
Liver Unit, Medical Science Department, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo (FG), Italy.

Article Received on 25/03/2021 **Article Revised on 15/04/2021** **Article Accepted on 05/05/2021**

ABSTRACT
The antipyretic and analgesic properties featuring paracetamol allow this drug to dominate the medical scenes since the late 19th century.

Nowadays, while moving toward a patient-centered healthcare system, an increasing interest is dedicated to paracetamol administration in vulnerable subpopulations including children, pregnant women, and older people with comorbidities. The aim of this paper is to review the applications of a widely consumed drug worldwide and its appropriate use during lifespan by setting aside some common misconceptions and contrasting the spread of fake news. A customized multidisciplinary board including pediatrician, child and adolescent neuropsychiatrist, gynecologist, hepatologist, nephrologist, gastroenterologist, internal and geriatric physician was set up. By applying the most recent evidence in literature to corroborate the clinical suggestions, this review offers precise answers to specific hot clinical questions.

KEYWORDS: Paracetamol, acetaminophen, pain, pregnancy, elderly.

INTRODUCTION
Discovered in the late 19th century the N-acetyl-paraminophenol (APAP) or paracetamol was first synthetized from the reduction of p-nitrophenol with tin in glacial acetic acid by Morse.[1] After disappearing for a long time with no deepening by scientific community about medical uses, during the '50, it was rediscovered and commercialized only after its identification in the urines of patients who had taken phenacetin or acetanilide. These two synthetic, antipyretic analgesics dominated the drug market during the first 50 years of the 20th century, but after that period their use was strongly reduced in many countries due to the nephrotoxic side effects that both the prodrugs exhibited. Paracetamol started to tread the scenes of the USA pharmaceutical market when, in 1955, McNeil Laboratories commercialized it as an "elixir for children", while it was approved for sale without a prescription only four years later in 1959. In 1961, the same company launched a version for adult and since that time paracetamol has become the most popular antipyretic and non-opioid pain-relieving drug.

Thanks to its consistent safety profile, paracetamol is nowadays the elective and safely worldwide used drug for fever and pain with a superior side-effect profile to other analgesics and therapeutic indications from childhood to late age.

The OTC selling statistics list spread by the Italian Ministry of Health for the second semester of 2019, saw paracetamol 500mg tablet at the first place, with more than two million pill packs sold.[2]

In Italy, the 1000 mg dose can be purchased only under medical prescription and the administration of paracetamol must not exceed the threshold dose of 3000 mg per day for adults.

Although paracetamol was commercialized and used for more than half a century, not all its mechanisms of action have been until now discovered and elucidated. While paracetamol analgesic and antipyretic properties link this molecule to non-steroidal anti-inflammatory drugs (NSAIDs), some other peculiar features prevent to ascribe it to this class. The molecule exhibits a weak anti-inflammatory activity and on the contrary of NSAID class drugs leading to many side effects, it is preferred because of its better tolerance.[3] Paracetamol pharmacology and toxicology is partially shared with NSAIDs with the basic pharmacological effects mainly relying on the suppression of prostaglandin (PG) production. Differently from NSAIDs that act by inhibiting cyclooxygenase (COX) through competition with arachidonic acid for the active site of the enzyme, paracetamol activity consists in reducing a ferryl protoporphyrin IX radical cation that, in turn, generates tyrosine radicals in the place of cyclooxygenase.[3][4] This mechanism with a fundamental importance for the oxidation of arachidonic acid, results in the inhibition of PG production but seems to act only under specific conditions that are dependent on the peroxide tone.[5] The peroxide tone evaluation led to suppose a selectivity of paracetamol on isoenzyme COX-2. It is now evident that when concentrations of arachidonic acid are low, the COX-2 pathway is activated in preference to the isoenzyme COX-1 pathway.[6] As a consequence, at the therapeutic plasma concentration range, paracetamol generally appears to be a selective COX-2 inhibitor in vitro. [7] To date, other research efforts are needed to understand the not completely clarified role of COX isoenzymes, but several evidences suggest that paracetamol acts not only through cyclooxygenase pathways.

A central effect via cannabinoid and vanilloid receptors (TRPA1, TRPV)[8][9] has been studied together with the interfering mechanism with the nociception at the spinal level that acts through the inhibition of the L-arginine-nitric oxide (NO) pathway.[4][10]

A recent study based on functional neuroimaging shows how self-experienced pain and empathy for pain in others involve some overlapping neural circuits .[11][12] Paracetamol reduces both the perception of own physical pain and the discomfort caused by other people's suffering and unpleasantness of noise blasts.[13]

The reduction in paracetamol-induced activation of paralimbic cortical brain areas could also explain the consequent reduction in positive empathy and empathic sharing of other's pleasant experiences.[14] The neurochemical basis of a possible reduction in empathic behaviours in rats would seem to rely on a decrease in oxytocin and vasopressin levels in the prefrontal cortex and amygdalae.[15]

Paracetamol also involves endogenous opioid pathway as confirmed by opioid antagonist use.[16]

In a double blind randomized recent study published by Bershad et al. in 2018,[17] opioid- and non-opioid analgesics have been compared on responses to psychosocial stress in humans using the Trier Social Stress Test (TSST) or a non-stressful control task (NSCT) test. Interestingly, paracetamol has been shown to influence some components of psychological stress without dampening physiological responses. Some evidences support the possibility that it reduces affective responses by acting on inflammation process that commonly has a key role in contributing to psychiatric symptoms, including depression.[17][18]

Paracetamol is even able to interact with descending serotonergic pathways; there are evidences in mouse, rat and humans that the analgesic activity of the paracetamol and COX-2 inhibitors is dependent on intact central serotonin systems.[19] Furthermore, serotonin deficiency exacerbates paracetamol-induced liver toxicity in mice.[20]

Although the specific interaction mechanisms of paracetamol are still unclear, some studies also suggested a correlation between serotonin metabolism and gut-brain axis.[21] Because differences in host intestinal microbiota are increasingly recognised as a potential source of inter-individual variation in response to drugs and toxins, drug-induced changes in the gut brain axis represent a newly and interesting research field.

Variations in intestinal microbiota do not fully explain differential susceptibility to paracetamol-induced hepatotoxicity in mice, but intervention aimed at modifying intestinal microbiota would seem to support the treatment of patient with acute liver failure.[22]

The discovery of paracetamol multiple interactions with vanilloid, cannabinoid, serotonergic and opioidergic receptors modified our understanding of this molecule, thus revealing its entangled complexity with an action at spinal and supraspinal levels. Although these pain pathways have been deep studied for many years, paracetamol antinociceptive mechanism, based on enhancing multiple endogenous analgesic networks, well explains the reason why its complex interaction model remains yet uncompleted.

Pharmacokinetics and pharmacodynamics

Paracetamol pharmacokinetics has been well studied in animals and human.

Very little oral paracetamol is absorbed from the stomach and owing to this its use as a model drug for gastric emptying is part of many mechanistic studies where retarded or impaired gastric emptying occurs.[23]

With a half-life elimination of approximately two hours at therapeutic doses and with a peak concentration being achieved within 90 minutes, the larger part of absorption has been detected in the proximal portion of the small

intestine. Due to differences in normal physiologic factors such as gastrointestinal movement, the pharmacokinetic profile of paracetamol, when oral administrated, has inter-subject variability; paracetamol rate and extent of absorption in GI tract appears to be age-dependent.[24] From the lumen across the mucosal membrane the drug flows into the bloodstream by passive diffusion.

Paracetamol oral availability is dose-dependent and ranges from 70% to 90%[25] and its pharmacokinetic variability depends on the way of administration i.e., orally or intravenously. In postoperative pain management practices, paracetamol intravenous administration results in shortening the length of hospital stay, hospitalization costs, and reducing the average daily morphine equivalent dose.[26] In a recent study Mallama et al. reported how paracetamol route of administration, intravenously or orally, did not affect pain or any other postoperative outcome.[27]

Considering the widespread use of this analgesic in frail, comorbid and healthy older adults, and the potential changes the relative pharmacokinetic may undergone, geriatric patients deserve specific medical attentions.

Recently, based on selected studies and clinical trials on paracetamol pharmacokinetics parameters and safety, Mian and colleagues reported a decrease in clearance (CL) and volume of distribution (Vd) in frail older people.[24] According to the evidence that changes in paracetamol formation mostly occur in impaired conjugation rather than in the formation of oxidative metabolites, the same authors argued that there is no evidence supporting a higher incidence of hepatotoxicity in normal paracetamol dosage in older subjects.

Paracetamol is less involved in causing significant gastrointestinal (GI) mucosal injury, such as gastrointestinal bleeding or organ adverse effects of NSAIDs [28] and usually the initial choice for paracetamol administration instead of NSAID occurs when pre-existing gastrointestinal risk factors are present.[29]

Clinical evidences support paracetamol safety profile in gastrointestinal tract when compared with NSAIDs, among which only ibuprofen seems to show a comparable and safety profile.[30]

Moreover, some literature data indicate that concomitant use of NSAIDs and paracetamol does not cause an increase of safety outcome risk over the use of the drugs alone.[31] Higher doses of paracetamol were more likely linked to gastrointestinal AEs like those occurring with high-dose NSAIDs.[32]

Almost completely metabolized in the liver (90%) where it is conjugated with glucuronic acid (50-60%), sulfuric acid (25-35%) and cystine (approximately 3%), only a very small amount (2−9%) of paracetamol is excreted unchanged. The two non-toxic paracetamol derived metabolites glucuronide and sulphate conjugates are excreted as a minor and major parts in the bile and in the urine, respectively.[33]

At therapeutic doses the 5–10% is oxidized by cytochrome P450 (CYP450) and forms the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI)[34] that is subsequently neutralized by glutathione and excreted as cysteine and mercapturate metabolites by the kidney. Cytochrome P450 enzyme activity is needed to produce the reactive metabolites of paracetamol NAPQI, but can be also induced by concomitant drug or herbal preparation use.[35]

In case of the recommended dosage is exceeded, or when the CYP2E1 capacity for glucuronidation and sulfation is saturated, increased amounts of NAPQI are formed.[35]

In case of intentional or unintentional overdoses paracetamol effects can lead to severe liver injury and even acute liver failure (ALF), a rare disorder characterized by high levels of aminotransferases (1000 IU/ml) and low levels of bilirubin.[36] Many factors can influence the severity and the outcome of liver failure and include concomitant alcohol abuse, drug-to-drug interactions and nutritional status; in patients with hepatic injury and chronic liver disease the serum half-life of paracetamol is prolonged of approximately 2 hours.[37]

A safety issue is whether therapeutic doses can cause liver injury in vulnerable patients. Among hepatotoxicity risk factors, malnourishment is the main condition that may predispose frail patients to related liver AEs, so it would be more prudent for high-risk frail older (with low weight or renal and hepatic impairment) to start with lower doses or reduce the dose frequency.[38]

No increased activity of P450 has been reported in patients with chronic liver disease and this pathologic status does not influence hepatic levels of glutathione. Consequently, paracetamol 1000 mg can be used at the standard 8 hours interval in patients with mild to moderate liver dysfunction (Class A+B according to Child-Pugh classification) after a careful analysis of patient-specific factors (Table 1).[39][40]

Table 1. Paracetamol indications at recommended dosage (3g/day) by age and specific pathological conditions.

Patient age or physiologic/pathologic condition	Indication in healthy/pathologic subset	Use in clinical practice
Children	From birth 10/15 mg/kg/dose	- Fever and pain - Postoperative pain - Procedural pain
Pregnant women	Maximum 3gr/die only in case of real need, under the direct control of the doctor, for a short period and at the lowest effective dose	- Fever and mild pain
Adult	Maximum 3 gr/die	- Fever - Pain - Headache - Small surgical interventions - Postoperative pain
Elderly	- Maximum 3gr/die - Comorbid patients - Start with a low dose and reduce dose frequency in high-risk and frail older patients (low weight or renal and hepatic impairment)	- Fever - OA pain related (even together with NSAIDs to reduce their toxicity - Cancer pain (mild pain on first step or together with weak opioids for opioid sparing)
Liver disease	Patients with mild-moderate liver dysfunction	- Fever and mild pain
Kidney disease	Dialysis patients	- Fever and mild pain
Cancer	Initial treatment stages	- Fever and mild pain

Together with drug overdose, the major risks for hepatic adverse effects are related to alcohol consumption. A recent study based on a large alcohol consumer cohort evidences that moderate/high alcohol consumption worsens the presentation and outcome of both paracetamol acute liver injury and acute liver failure.[41]

Renal dysfunction due to renal tubular necrosis may rarely occur in case of paracetamol severe poisoning[42] whereas liver functionally is much more easily compromised. Urinary excretion of unchanged paracetamol is only 1–4 % ; the great part is eliminated as paracetamol-glucuronide or paracetamol-sulphate.[43] In case of extracorporeal clearance of paracetamol, as occurring in patients undergoing dialysis, no dose modification is required and the drug continues to be the preferred analgesic, due to the sodium retentive effect of NSAIDs.[44]

Pakravan et al. consider the elevated creatinine concentrations, increased in case of severe paracetamol toxicity, to have a high prognostic value in patients candidate for an immediate transfer to the liver unit.[45] Also hyperlactataemia is considered a death predictor factor in acetaminophen-induced fulminant hepatic failure[46] and the sustained low-efficiency dialysis (SLED) appeared to improve acid–base status, decrease lactate and decrease paracetamol concentrations.[47] In patients requiring renal dialysis support, a continuous monitoring is needed also after the acetylcysteine antidote administration.

Hot clinical questions

As highlighted in the last Italian competent authority for drugs (AIFA) report in 2018,[48] attention has been paid to drug consumption among specific more vulnerable subpopulations: paediatrics, geriatrics and pregnant women. The aim of the below reported paragraphs is to shed light on paracetamol clinical use in these vulnerable patient populations covering the whole lifespan.

All the clinical suggestions here reported rely on a multidisciplinary cooperation among medical specialists that participated to an ad hoc structured medical board.

Adequate dosage of paracetamol in children

Preferably administered orally, paracetamol is indicated by Italian paediatricians (98.3%) as the first choice treatment for the management of fever in children and according to the 2016 update of the Italian Society for Paediatrics' guidelines, paracetamol can be also used under the time threshold of 3 months and in case of dehydration.[49] For an optimal management of fever, as indicated by the 2016 update of the Italian Society of Paediatrics' guidelines a dose of 15 mg/kg every six hours (up to a maximum of 60 mg/kg) for children and a dose of 10 mg/kg/dose (up to a maximum of 40 mg/kg/day) for infants up to three months, are recommended (Table 1). Using these doses, a comparative study of paracetamol and NSAIDs (ibuprofen at a dose of 10 mg/kg/dose) found equivalent efficacy and tolerability.[50] Moreover, although few specific data in literature deal with the treatment of discomfort in children with fever, paracetamol appears to

be the most indicated and recommended pharmacological tool to achieve early symptomatic improvement during febrile illness.[51]

However, many paediatricians and caregivers underdose the medication in case of fever [52] and acute pain. [53] The administration of the correct paediatric dose of fever or pain-relieving drugs is of major importance.

Paracetamol suicidal misuse in adolescent

Paracetamol deliberate self-poisoning is a world-wide issue and it is cause of fatal hepatotoxicity in western countries, [54] especially among adolescents (15–19-year-olds)[55] and even childhood.[56] Some measures have been used to reduce overdose cases; both pack size and amount of drug in each tablet have been reduced in UK; consequently, although a decreased death percentage was observed, the problem was not completely solved.[57] Warnings on packs had little deterrent effect and further preventive measures should be considered.[58] In order to avoid misuse, parents should improve drug storage security at home and pharmacists should pay much more attention in checking high dose prescriptions.

In Italy, the 1000mg dose can be purchased only under medical prescription.

In those intended overdose cases qualifying for liver transplantation, the multidisciplinary assessment approach is based on psychiatric evaluation.[37]

Analgesic use related to catamenial disorders and pain: endometriosis underestimation in young women

The physiologic acute inflammatory response featuring ovulation, menstruation and delivery, finds its molecular bases on mast-cell releasing factors (bradykinins, vasoactive factors, histamine, serotonin, cytokines, and specialized-pro-resolving mediators) that disappear when tissue integrity is restored.[59][60][61] Menstrual cycle is a physiologic inflammatory process with limited time duration, finalized to restore a new endometrial layer ("resolving"); inflammation has a moderate intensity, appropriate for the ongoing renewal process, and causes mild and not debilitating pain. Primary dysmenorrhea is the pain associated with menstrual bleeding and although is mostly related to a good prognosis, it can be more impactful and unpleasant for some women.[62] During the menstrual period, more than one-third of women always or often experience menstrual cramps and about the 70% of them suffer from a variety of symptoms that include irritability, fatigue, backache, headache, leg pains, nausea, vomiting, and pain.[63]

Dysregulation of the inflammation resolution process can lead to a progressive uncontrolled chronic inflammation.[64] The more intense the inflammation, the stronger the intensity of perceived pain. Table 2 reports some general aspects featuring inflammation.

Table 2. Leading features of inflammation in physiologic and pathologic conditions.

Physiologic	Pathologic
finalized ("resolving")	a-finalized ("non resolving")
imited duration	chronic duration
limited intensity	variable intensity, with flares

Heavy menstrual bleeding and endometriosis are the most frequent aetiologies of severe/invalidating dysmenorrhea, causing a progressive impairing impact on the women daily life and requiring appropriate analgesics.

Both paracetamol and NSAIDs are useful for the treatment of primary dysmenorrhea pain. [65] NSAIDs analgesic power appeared to be more effective in relieving pain duration than paracetamol[66] but, due to their higher toxicity and adverse effects, it would be more favourable to combine lower NSAIDs doses with paracetamol.[67]

Invalidating dysmenorrhea may represent the key symptom of endometriosis, a common cause of infertility and chronic pelvic pain (CPP), located in the pelvic area and that lasts for 6 months or longer. Endometriosis is a disabling, underdiagnosed and undertreated estrogen-dependent disorder affecting young women, defined by the presence of functional endometrial tissue in the uterine cavity.[67] The ectopic endometrial tissue that responds to hormonal stimulation cyclically grows and sheds within the host tissues and/or in the peritoneum. The accumulated ectopic blood causes an acute cyclic inflammation together with worsening pain. If endometriosis is not diagnosed, inflammation persists and pain turns from acute and cyclic to continuous, chronic and finally neuropathic, a real disease per se.[68] Chronic Pelvic pain is the tip of the iceberg of tissue inflammation most frequently triggered by the cyclic menstrual shedding of endometriotic lesions. It will persist when inflammatory molecules production becomes chronic. The diagnostic delay between invalidating dysmenorrhea and endometriosis varies between 7 and 9 years and involves two contributing factors: the neglect of the biological bases of menstrual pain and the lack of "visible" endometriotic lesions for many years. Current diagnostic tools (pelvic echography, magnetic resonance and even laparoscopy, in cases of deep infiltrating endometriosis) are not always capable to detect endometriotic lesions, especially when smaller than two millimetres.[69]

As well as NSAIDs, paracetamol, effectively reduce dysmenorrhea but is insufficient for pain relief in women with a non-diagnosed endometriosis.[70]

The prolonged use of multiple analgesics without pain relief, and/or pain worsening and shifting from cyclic/periodic, to continuous, recurrent, chronic, and

progressive, should raise suspicion of the presence of endometriosis.

The intensity of pain parallels the intensity of the underlying inflammation, as in the real world the intensity of smoke is usually proportionate to the intensity of the fire that is provoking it. Therefore, the goal is to reduce the inflammation by reducing the predisposing, precipitating and maintaining factors in a multimodal, concerted strategy.[71]

Physicians should avoid the minimalistic symptomatic pain-relieving approach and be proactive in diagnosing the underlying conditions contributing to dysmenorrhea and/or CPP.

Paracetamol during pregnancy and infantile neuropsychiatric disorders

Drug consumption during pregnancy is not recommended unless the potential benefits for the mother justify the potential risks to the unborn. Pregnancy physiologic changes including plasma volume increase, cardiac output and glomerular filtration influence the drug pharmacokinetics together with a decreased gastric emptying time thus delaying the drug effect.[72]

An increased use of medications including potentially teratogenic drug has been found in pregnant women[73] and about the 5% of pregnant women use one or more addictive substances. Recent research data show that smoking tobacco or marijuana, taking prescription pain relievers, or using illegal drugs during pregnancy are associated with a double or even a triple risk of stillbirth.[74][75][76]

The consumption of paracetamol remains the first line for the treatment of pain and fever during pregnancy (Table 1) and more than half of the mothers reported its use.[77] Paracetamol, as other free unbound drugs, readily crosses the placenta and because of the interaction with the endocannabinoid and serotonin systems has been deepened together with the foetal exposures during pregnancy and child outcomes.

Nevertheless also maternal inflammatory cytokines cross the placenta in febrile conditions and may affect foetal brain development;[78] similarly, the use of tobacco or other substances and the concurrent intake of alcohol might contribute in creating a substantial bias that affects the detection and evaluation of the analgesic effect of paracetamol and other OTC drugs during pregnancy.

Studies in mice during neonatal brain development reported that the drug affects the cognitive function.[79] However, no association between paracetamol administration during pregnancy and decreased neurodevelopmental performance or emotional/behavioural has been found by Tovo-Rodrigues and colleagues after evaluating neurological parameters at the end of the first and the second year of life, respectively.[80]

In the last five years an increasing number of papers dealing with the association of long-term paracetamol use and child neuropsychiatric disorders, but literature is not concordant in attributing a causal implication of paracetamol prenatal consumption on the onset of neuropsychiatric disorders.[81][82]

In a Norwegian sibling-controlled cohort study, children prenatally exposed to short-term use of paracetamol (1–27 days) showed poorer gross motor outcomes. In the same study, children exposed for more than 28 days showed impairments in communication, externalizing behaviour and internalizing behaviour.[83] Ji and colleagues found that cord biomarkers of foetal exposure to paracetamol were associated with significantly increased risk of childhood ADHD and autism in a dose dependent manner.[84]

Increased risk of ADHD diagnosis was primarily associated with first-trimester fever and repeated fever episodes while different disorders may potentially result from variation in exposure across pregnancy periods.[85] On the contrary, recent scientific evidences do not support a causal relation between the onset of the psychiatric disorder and the drug consumption.[82] Gustavson et al. showed how maternal fever in early pregnancy may be a risk factor for ADHD and inattention problems and argued that this risk is neither mitigated nor inflated by use of paracetamol.[86] Masarwa et al. claimed that unmeasured confounding may explain the previously reported association between paracetamol use during pregnancy and risk of ADHD.[82][87]

Although drug prescription during pregnancy deserves greater attention especially in the first weeks, the risk for underdosing is also a factor to be taken into account: inadequate pain management consequences, including both physiological and psychological factors weighing on the mother and the child, should worry more than the potential side effects of paracetamol itself.[88]

Pain treatment should be tailored to the lowest therapeutic dose for short time also in the second and third trimesters of pregnancy when posture changes lead to biomechanical effects and related pain is associated with increased consumption of drugs.[89]

NSAIDs administration should be avoided in the third trimester while, to date, paracetamol would seem to be safe and tolerated without risk.[90]

Throughout the pregnancy women must follow physician medical advices before taking any medications. When prescribing pain medicines to pregnant women, clinicians should follow the drug package insert.[91] In treating fever and pain, the Italian Medicines Agency

reported paracetamol as first choice drug during pregnancy and breastfeeding.[92]

Perimenopausal symptomatic hand/feet OA, refractory to standard symptomatic management

Osteoarthritis (OA) is known to be a major cause of pain and disability; it is a sex- and age-linked disease and statistically increases after the fifth decade and triples in women compared to men.

The first phase is a joint progressive inflammation, appropriately defined as "ostheoarthritis", followed by a progressive degenerative subversion of the joint "cytoarchitecture", with joint instability, restricted movements, deformity, and progressive functional impairment.

Due to the strict connection with estrogenic fluctuations and levels,[93] women are more likely to develop synovial inflammation (consequent to estrogenic deficiency) and bone re-modelling. Women's joints are very rich in estrogenic receptors. Premenopausal cyclic estrogenic fluctuation first, and then the loss of estrogen may trigger a powerful inflammatory reaction, particularly in the small joints of hands and feet. In addition, about the 25% of women have a genetically determined, familial polymorphism in the gene codifying for the estrogenic receptor that increases the joint inflammatory response to estrogens fluctuation and loss.[94] OA becomes even more dramatic and disabling in case of early menopause, when the anticipated estrogenic deficiency may lead to an earlier activation of the inflammatory process.

Paracetamol is widely used as a first-line analgesic in OA. The 2019 update of the Italian Society for Rheumatology clinical practice guidelines for the diagnosis and the management of knee, hip and hand osteoarthritis recommends paracetamol (up to 3g/day) as an effective initial oral analgesic for the treatment of mild to moderate pain.[95] Oral NSAIDs are recommended at the lowest effective dose and for the shortest duration in patients who inadequately respond to paracetamol administration.[95]

Paracetamol may result inadequate in the advanced stages of the OA of the hand which is a progressive common musculoskeletal condition affecting women in the age of the menopause. Since the first decades of the 19th century the "arthritis of the menopause" has been included among degenerative arthritis.[96]

Inflammation is particularly severe during the first two years after the menopause: this step is known as the "window of opportunity", when a timely and appropriate menopausal hormonal therapy (MHT) may modulate and reduce the progression of the disease from inflammatory to degenerative, avoiding a parallel pain shifting from acute to chronic. Some clinical evidences support the therapeutic effect of MHT therapy,[97] but to date it is not recommended as the first-line treatment.

The medical board here involved believes that further studies are needed in order to better determine the correct timing for the MTH replacement therapy administration. Specifically, more efforts are needed in treating patients presenting an aggressive, painful and invalidating perimenopausal hand/feet OA onset, accompanied by severe pain and a more rapid joint tissue destruction and deformity.

A timely MHT should be considered, in the very first phases of acute menopausal joint pain, when the "window of therapeutic opportunity" is still well opened, especially in families with genetic/familial OA of small joints; MHT makes possible to modulate/reduce the progression of OA together with its associated invalidating inflammation, movement impairment and pain.

Are elderly patients at greater risk of paracetamol adverse effects?

Likewise, other vulnerable "special populations", elderly patients deserve medical attention and clinical measures aimed both at checking the effect of multiple drug consumption (poly-pharmacotherapy) and lowering the related economic burden impacting on healthcare systems. The SIMPATHY European project (https://ec.europa.eu/eip/ageing/news/simpathy-project-tackle-polypharmacy-elderly_en. 2016), "Polypharmacy Management by 2030" recognizes polypharmacy to be a growing problem as population longevity and the incidence of multimorbidity are increasing.

Demographic indices by the Italian National Census Bureau (ISTAT) are in line with other Countries reporting an increasing percentage of drug consumption among 65-94 aged adults.

As reported by the Italian medicines agency (AIFA) elderly patients aged 65 use six/seven different drugs with a maximum of 7.7 drugs in elderly Italians aged 85.[92] A word-wide effort is moving towards a reduction of drug consumption in multimorbid geriatric patients that are at a higher risk of obesity, cerebrovascular, cardiovascular, renal and coagulation system disorders.

The achievement of good pain control in elderly patients is not a simple task, but it is necessary because of the high percentage of frail older people who demand for effective and safe analgesics.

Literature data are discordant in assessing paracetamol supremacy effect when compared with COXIB and NSAIDs in osteoarthritis pain relief. The excellent safety of paracetamol at therapeutic doses and the high percentage of elderly people (increasing with age) expressing positive preference, have contributed in rising its good reputation, and a recent systematic review and meta-analysis on the management of osteoarthritis in elderly, suggested its oral administration as fist line treatment together with NSAIDs topical use.[98]

The 2019 update of the Italian Society for Rheumatology guidelines for the diagnosis and management of knee, hip and hand osteoarthritis recommends preferring paracetamol in elderly patients because of its relative safety in comparison with NSAIDs.[95]

Besides considering the paracetamol AEs, some recent perspectives face the possibility to reduce medication impact on older and frail patients.

In order to reduce potentially inappropriate medications in frail older adults, with limited life expectancy, a recent tool including 27 criteria namely the STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy), has been developed but paracetamol is not among the drugs considered by most respondents to be discontinued[99] and despite the heterogeneity of elderly patient health conditions, it is not necessary to reduce the maximum dosage of 3 grams per day (Table 1).

Paracetamol is safe for elderly patients but the administration of other analgesics like NSAIDs and opioids in case of severe pain must be pondered. Pain intensity guides the proper selection of analgesics in frail older patients with comorbidities. In case of severe pain, strong opioids administration can be suggested and associated with improved function. As reported by Malec and Shega,[100] individual specific needs in comorbid older patients treated with opioids have to be necessarily included in a dedicated and continuous monitoring approach.

Although not related to the aim of this review, another main topic of analgesia that deserves just a brief mention is the cancer pain management.

Among recommendations for cancer pain relief in older people, the World Health Organization recommended the usage of non-opioid analgesics (paracetamol or NSAIDs) in the first step, for mild pain and together with a weak opioid in moderate pain (Table 1).[89]

As stated in an updated Cochrane library article, there is high uncertainty about the impact of paracetamol for treating cancer pain.[101] Likewise based on 2017 Cochrane review, there is no strong evidence in supporting or refuting the use of NSAIDs alone or in combination with opioids for the treatment of mild cancer pain. Because of NSAIDs significant toxicity it is necessary to monitor and reassess their long-term use.[102]

Noteworthy, in clinical practice, opioid-sparing adjuvants are used in common multimodal analgesia in cancer pain and postoperative pain management. Most of opioid AEs are in fact dose-related and the co-administration of paracetamol mitigate them.

In order to properly balance pain relief and AEs in elderly patient with comorbidities, frequent re-evaluation of dosage at various steps of analgesic therapy with drugs stronger than paracetamol and with a less safe profile, is needed.

Drug to (not only) drug interactions

Paracetamol is not itself directly toxic but any toxicity is due to its intermediate metabolites. Because polypharmacy both impact on healthy and specific population at all ages, the possibility of drug-drug interactions must be evaluated as a real problem.

The inducers of CYP2E1 and CYP1A2 may enhance the production of NAPQI and, consequently, increase the fraction of paracetamol oxidized to NAPQI.

The list of paracetamol drug-drug know interaction counts dozens of molecules and active substances and it is not to be forgotten that a huge number of drugs contain paracetamol in their formulation.

Due to short therapy duration in acute disease, serious adverse drug interactions with paracetamol are rarely reported, [103] but the amount of doses for extended periods increase with chronicity.

With the aim to elucidate paracetamol/warfarin competition in oxidative and nonoxidative pathways, two studies proved a different potency of the two warfarin isomers (L- and R-warfarin) and proposed that paracetamol can compete with the R-warfarin isomer, resulting in an increasing concentration of the more potent S-isomer.[104]

In geriatric patients an American study proved that the simultaneous administration of oral anticoagulant warfarin and daily use of moderate-high doses of paracetamol (2-4 grams), after two week of paracetamol administration, reveals a significant clinical interaction between the two drugs[104] with a consequent high haemorrhagic risk factor.

In a recent study on 104 elderly patients administered with a dose higher than 3 g/day a low percentage of drug-drug interaction (10%) has been detected.[105] As suggested by studies on model organisms, other confounding factors may contribute to the DDI development as shown for the synergistic effects observed in combination with NSAID.[106] About the mechanism, it has been suggested that paracetamol does not have sufficient antiplatelet effect to potentiate the anticoagulant effect of warfarin and that this interaction is due to a decrease in vitamin K dependent clotting factors.[107]

Despite cytochrome P450 inducers including carbamazepine, phenobarbital and isoniazid may theoretically lead to increased levels of NAPQI when combined with paracetamol, clinical complications are rare.[108]

With the new direct-acting antiviral agents-based HCV treatment, a potential risk of drug-drug interaction (DDI) exists in patients using oxycodone in combination with paracetamol, when regimens containing protease inhibitors are used to treat HCV infection. Oxycodone is metabolised by CYP3A4 and CYP2D6 and recent evidences show that the combination of oxycodone and paracetamol is more effective than oxycodone alone.[108]

Protease inhibitors are weak inhibitor of CYP3A4. However, since oxycodone has a narrow therapeutic window, its increased levels could increase or prolong the related AEs and hence may cause respiratory depression. Patients receiving oxycodone and any CYP3A4 inhibitor need to be clinically monitored.

Also, possible interactions with herbal preparations may have potential AEs on hepatic, renal functions and coagulation.[109] The globalization of the food habits opens the way to new spices and herbal preparations that can be also used in self-medication approaches. As a consequence, other molecule and drug interactions need to be explored.

Recently, FL83B mouse hepatocytes were used as an in vitro model for hepatotoxicity induced by paracetamol and demonstrated that a piperine-enhanced curcuminoid preparation administration, concomitant to paracetamol, is unlikely to result in a clinically significant interaction involving CYP3A, CYP2C9 conjugation enzymes.[110]

CONCLUSIONS

Paracetamol excellent safety at therapeutic doses makes it the commonly used antipyretic and the first-line analgesic for mild to moderate pain. In case of multimodal analgesia, both for cancer pain and postoperative pain management, paracetamol is used as an adjuvant for opioid-sparing therapies.

The administration of paracetamol is also recommended for subjects belonging to vulnerable specific populations: children (even if younger than 3 months), pregnant women and frail/comorbid elderly patients. During pregnancy, under medical supervision, the drug consumption should be tailored to the lowest effective dose and to the shortest time possible. In older frail and comorbid patients with chronic pain the consumption should also be carefully monitored.

In order to ensure an adequate pain control in elderly patients suffering from moderate to severe cancer pain, paracetamol administration should not be eliminated: sparingly, carefully prescribed doses can be combined with opioids under physician consult.

Severe/invalidating dysmenorrhea and aggressive perimenopausal osteoarthritis less respond to conventional doses of paracetamol. This behaviour should alert physicians and help them in addressing targeted treatments for the progressive tissue destroying inflammation and the associated worsening pain.

To avoid dangerous drug to drug interactions particular attention must be paid to the consumption of drugs containing paracetamol in their formulation and herbal preparations used in self-medication approaches. Moreover, as stated by the World Health Organization, more efforts are needed for prevent suicidal intended misuse, especially among adolescents.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The authors acknowledge Claudia Laterza, MD of Sanitanova S.r.l., for medical writing and editorial assistance.

Funding information

This work has been supported by an unrestricted grant by Angelini S.p.A.

REFERENCES

1. Morse HN. Ueber eine neue Darstellungsmethode der Acetylamidophenole. *Berichte Dtsch Chem Ges John Wiley Sons, Ltd*, 1878; 11: 232–3.
2. Ministero della Salute, Direzione Generale della digitalizzazione, del sistema informativo sanitario e della statistica., http://www.salute.gov.it/imgs/C_17_bancheDati_14_3_0_file.pdf, 2019.
3. Jozwiak-Bebenista M, Nowak JZ. Paracetamol: Mechanism of action, applications and safety concern. *Acta Pol Pharm - Drug Res*.
4. Hinz B BK. Paracetamol and cyclooxygenase inhibition: is there a cause for concern? ; *Ann Rheum Dis*, 2012; 71: 20–5.
5. Graham GG, Davies MJ, Day RO, et al. The modern pharmacology of paracetamol: Therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*. Epub ahead of print, 2013. DOI: 10.1007/s10787-013-0172-x.
6. Murakami M, Naraba H, Tanioka T, et al. Regulation of prostaglandin E2 biosynthesis by inducible membrane-associated prostaglandin E2 synthase that acts in concert with cyclooxygenase-2. *J Biol Chem*. Epub ahead of print, 2000. DOI: 10.1074/jbc.M003505200.
7. Kis B, Snipes JA, Simandle SA, et al. Acetaminophen-sensitive prostaglandin production in rat cerebral endothelial cells. *Am J Physiol - Regul Integr Comp Physiol*. Epub ahead of print, 2005. DOI: 10.1152/ajpregu.00613.2004.
8. Mallet C, Barrière DA, Ermund A, et al. TRPV1 in brain is involved in acetaminophen-induced

antinociception. *PLoS One*. Epub ahead of print, 2010. DOI: 10.1371/journal.pone.0012748.
9. Andersson DA, Gentry C, Alenmyr L, et al. TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid Δ9-tetrahydrocannabiorcol. *Nat Commun*. Epub ahead of print, 2011. DOI: 10.1038/ncomms1559.
10. Björkman R, Hallman KM, Hedner J, et al. Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. *Pain*. Epub ahead of print, 1994. DOI: 10.1016/0304-3959(94)90001-9.
11. Lamm C, Decety J, Singer T. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *Neuroimage*. Epub ahead of print, 2011. DOI: 10.1016/j.neuroimage.2010.10.014.
12. Tully J, Petrinovic MM. Acetaminophen study yields new insights into neurobiological underpinnings of empathy. *J Neurophysiol*. Epub ahead of print, 2017. DOI: 10.1152/jn.00723.2016.
13. Mischkowski D, Crocker J, Way BM. From painkiller to empathy killer: Acetaminophen (paracetamol) reduces empathy for pain. *Soc Cogn Affect Neurosci*. Epub ahead of print, 2016. DOI: 10.1093/scan/nsw057.
14. Cankaya S, Oktem EO, Saatci O, et al. Paracetamol alters empathy scores in healthy and headache subjects: Functional MRI correlates. *J Clin Neurosci*. Epub ahead of print, 2020. DOI: 10.1016/j.jocn.2020.04.053.
15. Kandis S, Ates M, Kizildag S, et al. Acetaminophen (paracetamol) affects empathy-like behavior in rats: Dose-response relationship. *Pharmacol Biochem Behav*. Epub ahead of print, 2018. DOI: 10.1016/j.pbb.2018.10.004.
16. Rezende RM, França DS, Menezes GB, et al. Different mechanisms underlie the analgesic actions of paracetamol and dipyrone in a rat model of inflammatory pain. *Br J Pharmacol*. Epub ahead of print, 2008. DOI: 10.1038/sj.bjp.0707630.
17. Bershad AK, Miller MA, Norman GJ, et al. Effects of opioid- and non-opioid analgesics on responses to psychosocial stress in humans. *Horm Behav*. Epub ahead of print, 2018. DOI: 10.1016/j.yhbeh.2018.04.009.
18. Müller N. Immunological aspects of the treatment of depression and schizophrenia. *Dialogues Clin Neurosci*.
19. Pickering G, Estève V, Loriot MA, et al. Acetaminophen reinforces descending inhibitory pain pathways. *Clin Pharmacol Ther*. Epub ahead of print, 2008. DOI: 10.1038/sj.clpt.6100403.
20. Zhang J, Song S, Pang Q, et al. Serotonin deficiency exacerbates acetaminophen-induced liver toxicity in mice. *Sci Rep*. Epub ahead of print, 2015. DOI: 10.1038/srep08098.
21. Stasi C, Sadalla S, Milani S. The Relationship Between the Serotonin Metabolism, Gut-Microbiota and the Gut-Brain Axis. *Curr Drug Metab*. Epub ahead of print, 2019. DOI: 10.2174/1389200220666190725115503.
22. Possamai LA, Mcphail MJ, Khamri W, et al. The role of intestinal microbiota in murine models of acetaminophen-induced hepatotoxicity. *Liver Int*. Epub ahead of print, 2015. DOI: 10.1111/liv.12689.
23. Srinivas NR. Acetaminophen absorption kinetics in altered gastric emptying: Establishing a relevant pharmacokinetic surrogate using published data. *J Pain Palliat Care Pharmacother*. Epub ahead of print, 2015. DOI: 10.3109/15360288.2015.1035834.
24. Mian P, Allegaert K, Spriet I, et al. Paracetamol in Older People: Towards Evidence-Based Dosing? *Drugs and Aging*. Epub ahead of print, 2018. DOI: 10.1007/s40266-018-0559-x.
25. Forrest JAH, Clements JA, Prescott LF. Clinical Pharmacokinetics of Paracetamol. *Clin Pharmacokinet*. Epub ahead of print, 1982. DOI: 10.2165/00003088-198207020-00001.
26. Hansen RN, Pham AT, Boing EA, et al. Reduced length of stay and hospitalization costs among inpatient hysterectomy patients with postoperative pain management including IV versus oral acetaminophen. *PLoS One*. Epub ahead of print, 2018. DOI: 10.1371/journal.pone.0203746.
27. Mallama M, Valencia A, Rijs K, et al. A systematic review and trial sequential analysis of intravenous vs. oral peri-operative paracetamol. *Anaesthesia*. Epub ahead of print, 2020. DOI: 10.1111/anae.15163.
28. García Rodríguez LA, Hernández-Díaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. *Arthritis Research*. Epub ahead of print, 2001. DOI: 10.1186/ar146.
29. Rahme E, Barkun A, Nedjar H, et al. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. *Am J Gastroenterol*. Epub ahead of print, 2008. DOI: 10.1111/j.1572-0241.2008.01811.x.
30. de Martino M, Chiarugi A, Boner A, et al. Working Towards an Appropriate Use of Ibuprofen in Children: An Evidence-Based Appraisal. *Drugs*. Epub ahead of print, 2017. DOI: 10.1007/s40265-017-0751-z.
31. De Vries F, Setakis E, Van Staa TP. Concomitant use of ibuprofen and paracetamol and the risk of major clinical safety outcomes. *Br J Clin Pharmacol*. Epub ahead of print, 2010. DOI: 10.1111/j.1365-2125.2010.03705.x.
32. Rahme E, Pettitt D, LeLorier J. Determinants and sequelae associated with utilization of acetaminophen versus traditional nonsteroidal antiinflammatory drugs in an elderly population. *Arthritis Rheum*. Epub ahead of print, 2002. DOI: 10.1002/art.10604.
33. Prescott L. Kinetics and metabolism of paracetamol and phenacetin. *British Journal of Clinical*

Pharmacology. Epub ahead of print, 1980. DOI: 10.1111/j.1365-2125.1980.tb01812.x.
34. Rumack BH. Acetaminophen hepatotoxicity: The first 35 years. In: *Journal of Toxicology - Clinical Toxicology*. 2002. Epub ahead of print, 2002. DOI: 10.1081/CLT-120002882.
35. Chen GW, Chen TY, Yang PM. Differential effect of herbal tea extracts on free fatty acids-, ethanol- and acetaminophen-induced hepatotoxicity in FL83B hepatocytes. *Drug Chem Toxicol*. Epub ahead of print, 2019. DOI: 10.1080/01480545.2019.1692026.
36. Tittarelli R, Pellegrini M, Scarpellini MG, et al. Hepatotoxicity of paracetamol and related fatalities. *Eur Rev Med Pharmacol Sci*.
37. Yoon E, Babar A, Choudhary M, et al. Acetaminophen-induced hepatotoxicity: A comprehensive update. *Journal of Clinical and Translational Hepatology*. Epub ahead of print, 2016. DOI: 10.14218/JCTH.2015.00052.
38. Wynne HA, Cope LH, Herd B, et al. The association of age and frailty with paracetamol conjugation in man. *Age Ageing*. Epub ahead of print, 1990. DOI: 10.1093/ageing/19.6.419.
39. Zapater P, Lasso De La Vega MC, Horga JF, et al. Pharmacokinetic variations of acetaminophen according to liver dysfunction and portal hypertension status. *Aliment Pharmacol Ther*. Epub ahead of print, 2004. DOI: 10.1111/j.1365-2036.2004.02022.x.
40. Schweighardt AE, Juba KM. A Systematic Review of the Evidence Behind Use of Reduced Doses of Acetaminophen in Chronic Liver Disease. *Journal of Pain and Palliative Care Pharmacotherapy*. Epub ahead of print, 2018. DOI: 10.1080/15360288.2019.1611692.
41. Puri P, Lee WM, Fontana RJ, et al. Alcohol consumption is associated with the severity and outcome of acute liver injury/failure. *Liver Int*. Epub ahead of print, 2020. DOI: 10.1111/liv.14327.
42. Blakely P, McDonald BR. Acute renal failure due to acetaminophen ingestion: A case report and review of the literature. *J Am Soc Nephrol*.
43. Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children, and adults. *Clin Pharmacol Ther*. Epub ahead of print, 1976. DOI: 10.1002/cpt1976193284.
44. Smyth B, Jones C, Saunders J. Prescribing for patients on dialysis. *Aust Prescr*. Epub ahead of print, 2016. DOI: 10.18773/austprescr.2016.008.
45. Pakravan N, Simpson KJ, Waring WS, et al. Renal injury at first presentation as a predictor for poor outcome in severe paracetamol poisoning referred to a liver transplant unit. *Eur J Clin Pharmacol*. Epub ahead of print, 2009. DOI: 10.1007/s00228-008-0580-9.
46. Schmidt LE, Larsen FS. Prognostic implications of hyperlactatemia, multiple organ failure, and systemic inflammatory response syndrome in patients with acetaminophen-induced acute liver failure. *Crit Care Med*. Epub ahead of print, 2006. DOI: 10.1097/01.CCM.0000194724.70031.B6.
47. Wong A, Tong RLK, Ryan L, et al. The use of sustained low efficiency dialysis (SLED) in massive paracetamol overdose. *Clin Toxicol*. Epub ahead of print, 2018. DOI: 10.1080/15563650.2017.1358366.
48. AIFA. L'uso dei Farmaci in Italia, Rapporto Nazionale Anno, 2018. *Oss Naz sull'impiego dei Med Ist Super di Sanità, Agenzia Ital del Farm*, https://www.aifa.gov.it/documents/20142/241052/OsMed_2018_Eng.pdf (2018).
49. Chiappini E, D'Elios S, Mazzantini R, et al. Adherence among Italian paediatricians to the Italian guidelines for the management of fever in children: A cross sectional survey. *BMC Pediatr*. Epub ahead of print, 2013. DOI: 10.1186/1471-2431-13-210.
50. Autret-Leca E, Gibb IA, Goulder MA. Ibuprofen versus paracetamol in pediatric fever: Objective and subjective findings from a randomized, blinded study. *Curr Med Res Opin*. Epub ahead of print, 2007. DOI: 10.1185/030079907X223323.
51. Doria M, Careddu D, Ceschin F, et al. Understanding discomfort in order to appropriately treat fever. *Int J Environ Res Public Health*. Epub ahead of print, 2019. DOI: 10.3390/ijerph16224487.
52. Goldman RD, Scolnik D. Underdosing of Acetaminophen by Parents and Emergency Department Utilization. *Pediatr Emerg Care*. Epub ahead of print, 2004. DOI: 10.1097/01.pec.0000113877.10140.d2.
53. Milani GP, Benini F, Dell'Era L, et al. Acute pain management: acetaminophen and ibuprofen are often under-dosed. *Eur J Pediatr*. Epub ahead of print, 2017. DOI: 10.1007/s00431-017-2944-6.
54. Gunnell D, Murray V, Hawton K. Use of paracetamol (acetaminophen) for suicide and nonfatal poisoning: worldwide patterns of use and misuse. *Suicide Life Threat Behav*. Epub ahead of print, 2000. DOI: 10.1111/j.1943-278X.2000.tb01098.x.
55. Pompili M, Masocco M, Vichi M, et al. Suicide among Italian adolescents: 1970-2002. *Eur Child Adolesc Psychiatry*. Epub ahead of print, 2009. DOI: 10.1007/s00787-009-0007-x.
56. Hedeland RL, Teilmann G, Thiesen LR, et al. Childhood suicide attempts with acetaminophen in Denmark: Characteristics, social behaviour, trends and risk factors. *Scand J Public Health*. Epub ahead of print, 2013. DOI: 10.1177/1403494812474122.
57. Hawton K, Townsend E, Deeks J, et al. Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: Before and after study. *Br Med J*. Epub ahead of print, 2001. DOI: 10.1136/bmj.322.7296.1203.
58. Simkin S, Hawton K, Kapur N, et al. What can be done to reduce mortality from paracetamol overdoses? A patient interview study. *QJM*. Epub ahead of print, 2012. DOI: 10.1093/qjmed/hcr135.
59. Elliott E, Hanson CK, Anderson-Berry AL, et al. The role of specialized pro-resolving mediators in

maternal-fetal health. *Prostaglandins Leukotrienes and Essential Fatty Acids*. Epub ahead of print, 2017. DOI: 10.1016/j.plefa.2017.09.017.
60. Duffy DM, Ko C, Jo M, et al. Ovulation: Parallels with inflammatory processes. *Endocrine Reviews*. Epub ahead of print, 2019. DOI: 10.1210/er.2018-00075.
61. Gold EB, Wells C, Rasor MON. The Association of Inflammation with Premenstrual Symptoms. *J Women's Heal*. Epub ahead of print, 2016. DOI: 10.1089/jwh.2015.5529.
62. Petraglia F, Bernardi M, Lazzeri L, et al. Dysmenorrhea and related disorders. *F1000Research*. Epub ahead of print, 2017. DOI: 10.12688/f1000research.11682.1.
63. Armour M, Parry K, Manohar N, et al. The Prevalence and Academic Impact of Dysmenorrhea in 21,573 Young Women: A Systematic Review and Meta-Analysis. *Journal of Women's Health*. Epub ahead of print, 2019. DOI: 10.1089/jwh.2018.7615.
64. Headland SE, Norling L V. The resolution of inflammation: Principles and challenges. *Seminars in Immunology*. Epub ahead of print, 2015. DOI: 10.1016/j.smim.2015.03.014.
65. Milsom I, Minic M, Dawood MY, et al. Comparison of the efficacy and safety of nonprescription doses of naproxen and naproxen sodium with ibuprofen, acetaminophen, and placebo in the treatment of primary dysmenorrhea: A pooled analysis of five studies. *Clin Ther*. Epub ahead of print, 2002. DOI: 10.1016/S0149-2918(02)80043-1.
66. Daniels SE, Paredes-Diaz A, An R, et al. Significant, long-lasting pain relief in primary dysmenorrhea with low-dose naproxen sodium compared with acetaminophen: a double-blind, randomized, single-dose, crossover study. *Curr Med Res Opin*. Epub ahead of print, 2019. DOI: 10.1080/03007995.2019.1654987.
67. Marjoribanks J, Ayeleke RO, Farquhar C, et al. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. *Cochrane Database of Systematic Reviews*. Epub ahead of print, 2015. DOI: 10.1002/14651858.CD001751.pub3.
68. Laux-Biehlmann A, D'hooghe T, Zollner TM. Menstruation pulls the trigger for inflammation and pain in endometriosis. *Trends in Pharmacological Sciences*. Epub ahead of print, 2015. DOI: 10.1016/j.tips.2015.03.004.
69. Bourgioti C, Preza O, Panourgias E, et al. MR imaging of endometriosis: Spectrum of disease. *Diagnostic and Interventional Imaging*. Epub ahead of print, 2017. DOI: 10.1016/j.diii.2017.05.009.
70. Leyland N, Casper R, Laberge P, et al. Endometriosis: Diagnosis and Management. *J Obstet Gynaecol Canada*. Epub ahead of print, 2010. DOI: 10.1016/S1701-2163(16)34589-3.
71. Graziottin A. Inflammation and Chronic Pelvic Pain: A Biological Trigger for Depression in Women? *J Depress Anxiety*. Epub ahead of print, 2014. DOI: 10.4172/2167-1044.1000142.
72. Pariente G, Leibson T, Carls A, Adams-Webber T IS. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. *PLoS Med*, 2016; 13(11): 1002160.
73. Engeland A, Bjørge T, Klungsøyr K, et al. Trends in prescription drug use during pregnancy and postpartum in Norway, 2005 to 2015. *Pharmacoepidemiol Drug Saf*. Epub ahead of print, 2018. DOI: 10.1002/pds.4577.
74. Wendell AD. Overview and epidemiology of substance abuse in pregnancy. In: *Clinical Obstetrics and Gynecology*. 2013. Epub ahead of print, 2013. DOI: 10.1097/GRF.0b013e31827feeb9.
75. Martin CE, Longinaker N, Mark K, et al. Recent trends in treatment admissions for marijuana use during pregnancy. *J Addict Med*. Epub ahead of print, 2015. DOI: 10.1097/ADM.0000000000000095.
76. Reutfors J, Cesta CE, Cohen JM, et al. Antipsychotic drug use in pregnancy: A multinational study from ten countries. *Schizophr Res*. Epub ahead of print, 2020. DOI: 10.1016/j.schres.2020.03.048.
77. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: A cross-sectional, multinational web-based study. *BMJ Open*. Epub ahead of print, 2014. DOI: 10.1136/bmjopen-2013-004365.
78. Ratnayake U, Quinn T, Walker DW, et al. Cytokines and the neurodevelopmental basis of mental illness. *Frontiers in Neuroscience*. Epub ahead of print, 2013. DOI: 10.3389/fnins.2013.00180.
79. Viberg H, Eriksson P, Gordh T, et al. Paracetamol (acetaminophen) administration during neonatal brain development affects cognitive function and alters its analgesic and anxiolytic response in adult male mice. *Toxicol Sci*. Epub ahead of print, 2014. DOI: 10.1093/toxsci/kft329.
80. Tovo-Rodrigues L, Carpena MX, Martins-Silva T, et al. Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. *Paediatr Perinat Epidemiol*. Epub ahead of print, 2020. DOI: 10.1111/ppe.12649.
81. Bauer AZ, Kriebel D, Herbert MR, et al. Prenatal paracetamol exposure and child neurodevelopment: A review. *Hormones and Behavior*. Epub ahead of print, 2018. DOI: 10.1016/j.yhbeh.2018.01.003.
82. Masarwa R, Platt RW, Filion KB. Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias? *Paediatr Perinat Epidemiol*. Epub ahead of print, 2020. DOI: 10.1111/ppe.12615.
83. Brandlistuen RE, Ystrom E, Eberhard-Gran M, et al. Behavioural effects of fetal antidepressant exposure in a Norwegian cohort of discordant siblings. *Int J Epidemiol*. Epub ahead of print, 2015. DOI: 10.1093/ije/dyv030.
84. Ji Y, Azuine RE, Zhang Y, et al. Association of Cord Plasma Biomarkers of in Utero

Acetaminophen Exposure with Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. *JAMA Psychiatry*. Epub ahead of print, 2020. DOI: 10.1001/jamapsychiatry.2019.3259.
85. Flinkkilä E, Keski-Rahkonen A, Marttunen M, et al. Prenatal inflammation, infections and mental disorders. *Psychopathology*. Epub ahead of print, 2016. DOI: 10.1159/000448054.
86. Gustavson K, Ask H, Ystrom E, et al. Maternal fever during pregnancy and offspring attention deficit hyperactivity disorder. *Sci Rep*. Epub ahead of print, 2019. DOI: 10.1038/s41598-019-45920-7.
87. Masarwa R, Levine H, Gorelik E, et al. Prenatal exposure to acetaminophen and risk for attention deficit hyperactivity disorder and autistic spectrum disorder: A systematic review,meta-analysis, and meta-regression analysis of cohort studies. *Am J Epidemiol*. Epub ahead of print, 2018. DOI: 10.1093/aje/kwy086.
88. Dunwoody CJ, Krenzischek DA, Pasero C, et al. Assessment, Physiological Monitoring, and Consequences of Inadequately Treated Acute Pain. *Pain Manag Nurs*. Epub ahead of print, 2008. DOI: 10.1016/j.pmn.2007.11.006.
89. WHO, https://www.who.int/ncds/management/palliative-care/Cancer-pain-guidelines-Annex-3.pdf?ua=1.
90. Black E, Khor KE, Kennedy D, et al. Medication Use and Pain Management in Pregnancy: A Critical Review. *Pain Practice*. Epub ahead of print, 2019. DOI: 10.1111/papr.12814.
91. FDA, https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-has-reviewed-possible-risks-pain-medicine-use-during-pregnancy.
92. AIFA, https://www.aifa.gov.it/en/-/farmaciegravidanza.
93. Martín-Millán M, Castañeda S. Estrogens, osteoarthritis and inflammation. *Joint Bone Spine*. Epub ahead of print, 2013. DOI: 10.1016/j.jbspin.2012.11.008.
94. Liu W, Shao FM, Yan L, et al. Polymorphisms in the gene encoding estrogen receptor alpha are associated with osteoarthritis in Han Chinese women. *Int J Clin Exp Med*.
95. Parisi S, Bortoluzzi A, Sebastiani GD, et al. The Italian society for rheumatology clinical practice guidelines for rheumatoid arthritis. *Reumatismo*. Epub ahead of print, 2019. DOI: 10.4081/reumatismo.2019.1202.
96. Cecil RL, Archer BH. Classification and treatment of chronic arthritis. *J Am Med Assoc*. Epub ahead of print 1926. DOI: 10.1001/jama.1926.02680100025007.
97. Mahajan A PR. Menopause and Osteoarthritis: Any Association ? *J Midlife Health*, 2018; 171–172.
98. Stewart M, Cibere J, Sayre EC, et al. Efficacy of commonly prescribed analgesics in the management of osteoarthritis: a systematic review and meta-analysis. *Rheumatology International*. Epub ahead of print, 2018. DOI: 10.1007/s00296-018-4132-z.
99. Lavan AH, Gallagher P, Parsons C, et al. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): Consensus validation. *Age Ageing*. Epub ahead of print, 2017. DOI: 10.1093/ageing/afx005.
100. Malec M, Shega JW. Pain Management in the Elderly. Medical Clinics of North America. Epub ahead of print, 2015. DOI: 10.1016/j.mcna.2014.11.007. 2.
101. Wiffen PJ, Derry S, Moore RA, et al. Oral paracetamol (acetaminophen) for cancer pain. Cochrane Database of Systematic Reviews. Epub ahead of print 2017. DOI: 10.1002/14651858.CD012637.pub2. 3.
102. Derry S, Wiffen PJ, Häuser W, et al. Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. Cochrane Database of Systematic Reviews. Epub ahead of print 2017. DOI: 10.1002/14651858.CD012332.pub2. 4.
103. Hersh E V., Moore PA, Ross GL. Over-the-counter analgesics and antipyretics: A critical assessment. Clin Ther. Epub ahead of print 2000. DOI: 10.1016/S0149-2918(00)80043-0.
104. Parra D, Beckey NP, Stevens GR. The effect of acetaminophen on the international normalized ratio in patients stabilized on warfarin therapy. Pharmacotherapy. Epub ahead of print 2007. DOI: 10.1592/phco.27.5.675.
105. Kaas Oldenburg LI, Dalhoff KP, Sandoval LØ, et al. The Risk of Drug-Drug Interactions with Paracetamol in a Population of Hospitalized Geriatric Patients. J Pharm. Epub ahead of print 2020. DOI: 10.1155/2020/1354209.
106. Miranda HF, Puig MM, Prieto JC, et al. Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain. Pain. Epub ahead of print 2006. DOI: 10.1016/j.pain.2005.11.012.
107. Mahé I, Bertrand N, Drouet L, et al. Interaction between paracetamol and warfarin in patients: A double-blind, placebo-controlled, randomized study. Haematologica.
108. Toes MJ, Jones AL, Prescott L. Drug interactions with paracetamol. American Journal of Therapeutics. Epub ahead of print 2005. DOI: 10.1097/00045391-200501000-00009.
109. Abebe W. Herbal medication: Potential for adverse interactions with analgesic drugs. Journal of Clinical Pharmacy and Therapeutics. Epub ahead of print 2002. DOI: 10.1046/j.1365-2710.2002.00444.x.
110. Volak LP, Hanley MJ, Masse G, et al. Effect of a herbal extract containing curcumin and piperine on midazolam, flurbiprofen and paracetamol (acetaminophen) pharmacokinetics in healthy volunteers. Br J Clin Pharmacol. Epub ahead of print 2013. DOI: 10.1111/j.1365-2125.2012.04364.x.