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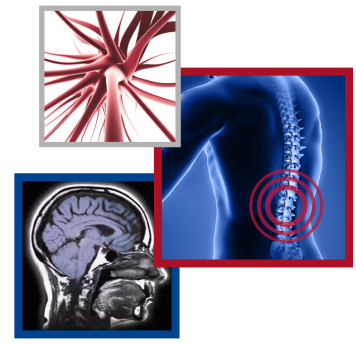
Pain Management



Paracetamol for multimodal analgesia

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Practice points

- Pain is a major cause of disability and suffering worldwide.
- A single analgesic drug does not provide effective pain control in many patients.
- Multimodal analgesia consists in using multiple drugs and techniques to improve efficacy and tolerability of pain treatment.
- Experimental preclinical and clinical evidence supports that paracetamol augments significantly the analgesic effects of anti-inflammatory, opioid and anti-neuropathic drugs in different clinical settings.

Pain and related disability remain a major social and therapeutic problem. Comorbidities and therapies increase drug interactions and side effects making pain management more compounded especially in the elderly who are the fastest-growing pain population. Multimodal analgesia consists of using two or more drugs and/or techniques that target different sites of pain, increasing the level of analgesia and decreasing adverse events from treatment. Paracetamol enhances multimodal analgesia in experimental and clinical pain states. Strong preclinical evidence supports that paracetamol has additive and synergistic interactions with anti-inflammatory, opioid and anti-neuropathic drugs in rodent models of nociceptive and neuropathic pain. Clinical studies in young and adult elderly patients confirm the utility of paracetamol in multimodal, non-opioid or opioid-sparing, therapies for the treatment of acute and chronic pain.

Plain language summary: Opioid and anti-inflammatory drugs are essential medications to relief pain; however, they may pose a serious health risk especially in elderly patients and in patients with medical conditions. Doctors are studying ways to reduce or eliminate their use. We wanted to see how well paracetamol works together with other painkillers to manage pain. Paracetamol (or acetaminophen) is one of the most prescribed medication for fever and pain. We found strong evidence that paracetamol given in association with other analgesic drugs enhances the pain relief in adult patients and in elderly adult patients, even though more studies are warranted in the latter. The use of paracetamol in combination with other analgesics is recommended by physicians and surgeons of different specialties.

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Keywords: analgesia • multimodal analgesia • paracetamol

Pain is cause of an enormous personal and social burden. The economic costs per year in terms of healthcare and lost productivity have been estimated at more than USD$650 billion in the USA and more than €300 billion in Europe [1,2]. As pain increases with age and the world's population is aging, the number of people living with pain and pain disability is expected to worsen in the near future [3]. The main goal of pain treatment is to provide clinically meaningful relief, improve the wellbeing and the functions of patients and reduce the side effects and complications related to treatment. A major goal is also preventing the transition from acute to chronic pain [4]. The clinical experience has shown that these goals are hard to achieve with a single agent or technique because patients experience pain from multiple mechanisms and safety and tolerability issues limit the drug efficacy. The aging process *per se*, diseases and pharmacological therapies may alter the pharmacokinetic and pharmacodynamic responses to drugs making pain control more difficult to achieve in the elderly and the comorbid patient [3].

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Given the complex neurobiology underpinning the pain and the associated symptoms (i.e., anxiety, depression, unrefreshing sleep, low energy), the available treatments are often limited by their efficacy and side effects. Many pain drugs act on the CNS and may negatively impact cognitive and vital functions [3,5–7]. Therefore, side effects often require a reduction of the dose decreasing thus treatment efficacy [3]. The multimodal analgesia (MMA) is based on the principle that the concurrent use of different analgesics will provide a superior analgesia in larger numbers of patients [5]. Ideally, an MMA agent should have a synergistic or an additive analgesic effect with other classes of pain drugs without cumulative side effects; it should enable the use the lowest dose possible of each drug without losing analgesia and minimizing side effects [5].

Paracetamol, N-acetyl-para-aminophenol (APAP), is an analgesic and antipyretic drug available worldwide that shows efficacy for mild-to-moderate pain [6,7]. Given orally APAP is readily absorbed from the gastro-intestinal tract and then undergoes liver metabolism mainly by glucuronidation and sulfation, and renal excretion [6]. It has complex mechanisms of action including the inhibition in peripheral tissues and in the CNS of cyclo-oxygenase activity (COX_1, COX_2, and COX_3), nitric oxide synthase and T-type $Cav_{3.2}$ calcium channels, and the direct or indirect activation of the cannabinoid CB_1 receptor, the transient receptor potential $TRPV_1$ or $TRPA_1$ receptors, the voltage-gated Kv_7 potassium channels, and serotoninergic receptors and pathways [6–11]. The volume of distribution and clearance of APAP decrease in an age-dependent fashion with high intersubject variability [12–16]. While early pharmacokinetic studies reported higher plasma levels of APAP in aged than in young subjects, recent investigations suggest a possible underdosing of APAP in elderly patients [12–16]. However, the pharmacodynamic targets of APAP probably also undergo age-related changes which may actually compensate for a potential underexposure and, this way, maintain efficacy of APAP during aging [17]. APAP has been administered in experimental and clinical settings through different routes including the intraperitoneal (IP), intrathecal (IT), intravenous (IV), oral (PO) and subcutaneous (SC) route [6–17]. Concerns involving the use of high doses of APAP have been associated with liver toxicity particularly in patients with liver or psychiatric diseases or malnourished [6,18].

This is a narrative review of the evidence on APAP for MMA.

Materials & methods

A literature search was conducted on adult human studies exploring Cinhal, Cochrane, Embase and Medline databases by using the following keywords: additive, analgesia, anticonvulsivant, antidepressant, anti-inflammatory, anti-neuropathic, multimodal, neuropathic, opioid, pain, paracetamol/acetaminophen, patient, mouse, rat, supra-additive, synergistic. Studies were included when the relative contribution of APAP to MMA could be inferred.

Results

Preclinical studies

The role of APAP for MMA has been formally determined in rodents in experimental nociceptive and inflammatory pain induced by exposure to noxious heat (i.e., tail flick test) or to irritant solutions (i.e., acetic acid writhing test, carrageenan test, formalin test, Freund's adjuvant test) or by a surgical incision. APAP for MMA in neuropathic rodent pain has been investigated in diabetic, genetic, toxic neuropathies and in traumatic myelopathies and neuropathies [19–42]. Results are summarized in Table 1. In almost all studies, APAP augmented synergistically the analgesia by anti-inflammatory, opioid, anticonvulsivant and antidepressant drugs.

Sandrini *et al.* demonstrated that the combination of low, inactive doses of APAP and morphine provided an antinociceptive effect in the hot plate test and decreased brain concentrations of dynorphin in the rat; pretreatment with the opioid antagonist naloxone abolished APAP antinociception both in hot-plate and in the first but not in the second phase of the formalin test [19]. Using the isobolographic analysis Janovsky and Krsiak showed that the opioid codeine had sub-additive interactions with COX_2 inhibitors and supra-additive analgesic effects with ibuprofen or APAP in the mouse acetic acid-induced abdominal constriction test, the writhing test [20]. Miranda *et al.* calculated the effects of IP or PO administration of APAP on the dose that produced 50% antinociception (ED_{50}) of eight different NSAIDs in the mouse writhing test; all the combinations were synergistic, the experimental ED_{50s} being significantly smaller than those theoretically calculated [21]. They also showed that IP or IT co-administration of APAP and of the opioid tramadol had a strong analgesic synergism that was not modified by opioid antagonism with naltrexone [22]. In the writhing test, APAP was synergistic also with matrine a natural alkaloid with affinity for κ– and μ– opioid receptors [23]. Zapata-Morales *et al.* evaluated the effects of fixed-dose combinations (FDC) of APAP and tapentadol (1–1, 1–3 and 3–1) in the formalin-pain in mice; the APAP-tapentadol FDCs 1-1 and

Table 1. Interactions of paracetamol with other analgesics in experimental pain models.

First author, year of publication	Species	Pain test	Drug	Drug class	Interaction	Opioid antagonism
Nociceptive pain						
Cabañero and Maldonado, 2021	Mouse	Incision test	Nefopam	Monoamine reuptake inhibitor/glutamate modulator	Synergistic	NT
Dai, 2021	Mouse	Writhing test	Matrine	Opioid	Synergistic	NT
Girard, 2011	Mouse	Writhing test Formalin test	Nefopam	Monoamine reuptake inhibitor/glutamate modulator	Synergistic Additive	NT
	Rat	Incision test Carrageenan test			Synergistic	
Janovsky and Krsiak, 2011	Mouse	Writhing test	Codeine	Opioid	Synergistic	NT
Li, 2021	Rat	Carrageenan test	Rotigonine	Dopamine agonist	Synergistic	NT
Miranda, 2006	Mouse	Writhing test	Diclofenac Ibuprofen Ketoprofen Meloxicam Metamizol Naproxen Nimesulide Parecoxib Piroxicam	NSAID	Synergistic	No
Miranda, 2021	Mouse	Writhing test	Tramadol	Opioid/monoamine reuptake inhibitor	Synergistic	NT
Sandrini, 2001	Mouse	Formalin test	Morphine	Opioid	Synergistic	Yes
Tomic, 2021	Mouse	Writhing test	Oxcarbazepine	Sodium channel blocker	Synergistic	NT
	Rat	Carrageenan test				
Mititelu-Tartau, 2015	Mouse	Tail flick test Writhing test	Pregabalin	Gabapentinoid	Synergistic	NT
Yoshizawa, 2020	Mouse	Freund's adjuvant	Tramadol	Opioid/Monoamine reuptake inhibitor	Synergistic	Yes
Zapata-Morales, 2018	Mouse	Formalin test	Tapentadol	Opioid/Norepinephrine reuptake inhibitor	Additive Synergistic	Yes
Neuropathic pain						
Déciga-Campos and Ortíz-Andrade, 2015	Rat	Streptozotocin diabetes/acetone test/formalin test	N-palmitoylethanolamide	Nuclear factor agonist/ Cyclo-oxygenase inhibitor	Synergistic	NT
Garrido-Suarez, 2021	Rat	Chronic constriction nerve injury/formalin test	Amtryptiline	Monoamine reuptake inhibitor	Synergistic	NT
Gong, 2011	Rat	Streptozotocin diabetes/von Frey test/tail-flick test	Tramadol	Opioid/monoamine reuptake inhibitor	Additive Synergistic	
Li, 2021	Rat	Carrageenan test	Rotigonine	Dopamine agonist	Synergistic	NT
Sato, 2020	Rat	Nucleus polposus radicular apposition/von Frey test	Tramadol	Opioid/monoamine reuptake inhibitor	Additive	NT
Shinozaki, 2015	Rat	Tibial neuroma transposition/carrageenan test	Tramadol	Opioid/monoamine reuptake inhibitor	Synergistic	Yes

NT: Not tested.

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the 3-1 produced additive effects, whereas the APAP-tapentadol 1–3 FDC showed an antinociceptive synergistic interaction [24].

A low analgesic dose of APAP (300 mg/kg) and an ineffective dose of the monoamine reuptake inhibitor and glutamente modulator nefopam (3 mg/kg) had additive or synergistic analgesic effects in the mouse writhing and formalin tests. The combination of a low analgesic dose of APAP (300 mg/kg) and of a non-analgesic dose of nefopam (3 mg/kg) significantly inhibited thermal-induced hyperalgesia in a rat postoperative incision model; a combination of a non-analgesic dose of APAP (30 mg/kg) and of a low analgesic dose of nefopam (10–30 mg/kg) abolished the tactile allodynia in the rat carrageenan test [25]. Recently, Cabañero and Maldonado assessed the effects of PO APAP and PO nefopam administered either alone or in combination in a murine model of postsurgical pain [26]. Both APAP and nefopam administered alone dose-dependently reduced postoperative hind paw withdrawal to von Frey filament stimulation and to radiant heat [26]. The doses of APAP and nefopam that achieved 18 and 35% inhibition of postsurgical mechanical and thermal nociception when administered individually, reached 75 and 95% pain relief when given in combination indicating that APAP and nefopam have strong synergistic effects [26]. APAP dose-dependently attenuated the paw withdrawal response from a hot plate in rats with a mild thermal injury [27]. The administration of either PO APAP or of IM microspheres loaded with the dopaminergic agonist rotigonine attenuated paw withdrawal to thermal and mechanical stimulation in the rat carrageenan pain test [29]. The combined administration of APAP and rotigonine produced an enhanced, synergistic analgesia in the same test [29].

Although variably effective by itself, APAP consistently enhanced the analgesic activity of anti-neuropathic drugs in neuropathic pain conditions [30–42]. In particular, APAP did not modify nociceptive responses evoked by noxious mechanical and electrical stimulation in traumatic and metabolic neuropathies (ie, sciatic nerve ligation and streptozotocin-induced diabetes) [30,31]. Administered to rats, APAP alone reduced the behavioral responses to the carrageenan pain but not to neuropathic pain from tibial neuroma transposition [32]. APAP, however, reduced significantly and in a synergistic manner the ED_{50} of the opioids tramadol and morphine in both inflammatory and neuropathic pain [32]. Also, a low dose of APAP suppressed mechanical pain hypersensitivity in rats with a spared nerve injury (ie, ligation of the tibial and peroneal nerve), without influencing the behavior in sham-operated rats [33]. Co-administered with tramadol, APAP almost abolished the withdrawal response to von Frey filaments in a rat neuropathic pain model obtained with the application of the nucleus polposus on the left L_5 dorsal root ganglion [35]. In the mouse, low doses of either tramadol (10 mg/kg) or APAP (100 mg/kg) did not produce an antinociceptive effect in neuropathic pain from a sciatic nerve lesion and in inflammatory pain from intraplantar injection of Freund's adjuvant; remarkably, however, their combination suppressed Freund's adjuvant-induced mechanical allodynia and their analgesic activity was attenuated by the opioid antagonist naloxone [38]. In rats, PO administration of APAP or of the tricyclic antidepressant amitriptyline produced a dose-dependent antinociception during the second phase of the formalin test model of neuropathic pain. A repeated treatment with either drug attenuated the mechanical allodynia induced by a nerve chronic constriction injury [10]. A combination treatment with amitriptyline and APAP showed a dose-dependent, synergistic, antinociceptive and antiallodynic effect [10]. Importantly, the amitriptyline-APAP combination prevented the nerve histopathological changes induced by chronic constriction, suggesting a possible neuroprotective activity and a mechanistic link for its antiallodynic effect [10]. Hama investigated the effects of APAP on neuropathic pain in spinal cord injured rats [39]. Although not analgesic itself, APAP exerted an additive antinociceptive effect with the opioid agonist tramadol and with the uncompetitive N-methyl-D-aspartate antagonist memantine on spinal neuropathic pain; in the same model APAP displayed a supra-additive synergistic analgesia when given with morphine or with the voltage-gated calcium channel ligand gabapentin [39].

Mititelu Tartau reported a synergistic effect between APAP and pregabalin on the mouse tail flick and writhing tests [40]. PO APAP (50–200 mg/kg) and PO oxcarbazepine (40–160 mg/kg) given in different combinations of their ED_{50} (1–8, 1–4, 1–3 and 1–2) produced a dose-dependent and synergistic anti-hyperalgesia in the mouse writhing test and in the rat carrageenan test [41]. A SC injection of either APAP or of the fatty nuclear factor agonist N-palmitoylethanolamide determined concentration-dependent, anti-neuropathic responses in the acetone and formalin tests in streptozotocin-diabetic rats [36]. The combined administration of APAP and N-palmitoylethanolamide produced a larger, synergistic analgesia [37]. IP injection of APAP and tramadol produced a dose-dependent antinociceptive effect in von Frey, hot plate and tail-flick tests in diabetic rats [38]. The isobolographic analysis showed a significant deviation of 50% maximum antinociceptive effect by APAP-tramadol combination in the tail-flick test [38].

Table 2. Comparative analgesic efficacy of intravenous and *per os* paracetamol.

First author, publication year	Population	Study	Patient number	Outcome
Antill, 2020	Elderly rib fracture	RCT	138	IV = PO: pNRS, ICU LOS
Furyk, 2018	Acute pain	RCT	87	IV = PO: pVAS, MMEs, ED LOS
Charlton, 2020	Abdominal and trauma pain	RETRO	80	IV >PO: pNRS
Furyk, 2018	Acute pain	RCT	87	IV = PO: pVAS, MMEs, LOS
Hansen, 2018	Cholecystectomy	RETRO	61.017	IV >PO: H LOS, costs, MMEs, PONV
Johnson, 2019	Cholecystectomy	RETRO	579	IV = PO: pNRS, MMEs
Marcotte, 2020	Colorectal resection	RETRO	91	IV = PO: pVAS IV >PO: MMEs
Plunkett, 2017	Cholecystectomy	RCT	60	IV = PO: $SPID_{24}$, MMEs
Wasserman, 2018	Colectomy	RETRO	181,640	IV = PO: MMEs; PO >IV on POD1
Bhoja, 2020	Sinus surgery	RCT	110	IV = PO: pVAS MMEs
Cain, 2020	Gynecologic oncology surgery	RETRO	353	IV = PO: MMEs
Hansen, 2018	Hysterectomy	RETRO	22.828	IV >PO: H LOS
Kor, 2020	Cystoscopy	RETRO	3566	IV = PO: pNRS; PO > IV, MMEs, PONV
Lombardi, 2020	Laparoscopic hysterectomy:	RCT	74	IV = PO: pNRS, MMEs
Wilson, 2019	Cesarean delivery	RCT	141	IV = PO: pVAS, sVAS, MMEs
Hickman, 2018	Total hip/knee arthroplasty	RCT	486	IV = PO: pVAS, MMEs, PACU LOS, H LOS
O'Neal, 2017	Total knee arthroplasty	RCT	174	NO effect of APAP
Pettersson, 2005	Coronary artery bypass graft	RCT	80	IV = PO: pVAS; PO > IV: MMEs
Politi, 2017	Total hip/knee arthroplasty	RCT	120	IV = PO: pVAS, MMEs
Stundner, 2019	Total hip/knee arthroplasty	RETRO	1.039.647	IV = PO
Suarez, 2018	Total knee arthroplasty	RCT	–	IV = PO: pVAS, MMEs
Westrich, 2019	Total hip arthroplasty	RCT	154	IV = PO: pNRS, MMEs, AEs
Wasserman, 2018	Colectomy	RETRO	181,640	IV = PO: MMEs, PO > IV on POD1

AE: Adverse event; ED: Emergency department; H: Hospital; ICU: Intensive care unit; IV: Intravenous; LOS: Length of stay; MME: Morphine milligram equivalent, opioid consumption; PACU: Post-anesthesia care unit; pNRS: Pain Numerical Rating Scale; PO: *per os*; POD1: Postoperative day 1; PONV: Postoperative nausea and vomiting; pVAS: Pain Visual Analogue Scale; RCT: Randomized controlled trial; RETRO: Retrospective study; sVAS: Satisfaction Visual Analogue Scale; $SPID_{24}$: 24-h postoperative sum of pain intensity difference.

Genetic mutations of SCN11A have been associated to the gain-of-function of $Na_V1.9$ sodium channels, painful small fiber neuropathies and familial episodic pain syndromes [37]. In mice carrying the SCN11A p. R222S mutation, APAP significantly reduced mechanical allodynia and thermal hypersensitivity in the von Frey filament test and tail-flick test [37]. In rats APAP alone exhibited also a significant anti-allodynic effect with a good therapeutic index in the chemotherapy neuropathic pain [34].

Clinical studies

Oral versus intravenous APAP

The efficacy of IV versus PO administration of APAP has been extensively investigated in retrospective studies (RETRO) and randomized-controlled clinical trials (RCTs) which are summarized in Table 2 [42–58]. The primary outcome was the pain intensity and satisfaction assessed with the different scales including the pain Numerical Rating Scale (pNRS), the pain and satisfaction Visual Analogue Scale (pVAS, sVAS), the 24-h postoperative sum of pain intensity difference ($SPID_{24}$), and the opioid consumption expressed as morphine milligram equivalent (MME). Secondary outcomes were costs, the length of stay (LOS) in the Emergency Department (ED), post-anesthesia care unit (PACU) and hospital (H; Table 2).

PO APAP undergoes a liver first-pass metabolism whereas IV APAP does not [6]. However, when comparable dosages are administered PO APAP was as effective as IV APAP in controlling acute trauma and postoperative pain [42–58]. Stagg analyzed nine studies to compare the relative efficacy of IV and PO APAP administered for postoperative analgesia [56]. Compared with PO, IV APAP was associated to a small reduction (0.5 points) of pain scores and opioid consumption [56]. A recent meta-analysis on 14 RCTs and 1695 participants concluded that route of APAP administration did not affect postoperative pain; quality of evidence was judged poor [57]. Stundner *et al.* reviewed data from 1,039,647 total hip arthroplasty/total knee arthroplasty (THA/TKA) procedures sampled from the Premier Healthcare claims database 2011–2016 and found a better outcome in patients treated with PO

than with IV APAP; specifically, IV and PO APAP reduced opioid dosage by, respectively 6.0 and 11% (compared with no APAP); further comparisons favored PO over IV APAP [58].

APAP for MMA

The concept of balanced, MMA was first introduced in the early 1990s by Kehlet *et al.* and was based on the premise that using a combination of opioid and nonopioid analgesics would improve pain control and reduce opioid-related side effects [59,60]. MMA and/or multidisciplinary approaches have since been supported by anesthesiology and pain societies. For acute pain, the American Society of Anesthesiologists task force strongly supports MMA with the routine use of perioperative non-opioid medications (ie, NSAIDs, COX_2 inhibitors and APAP) and regional anesthetic techniques. For chronic pain, the Pain Management Best Practices Inter-Agency Task Force recommends MMA within a multimodal approach with NSAIDs and APAP as first-line classes of medications [7]. Because of the recent opioid epidemic, non-opioid drugs including APAP gained further popularity within the context of MMA in the attempt of reducing opioid dosage and side effects [6,7,60,61]. A large number of RCTs have demonstrated that APAP MMA reduces pain scores and opioid dosage and adverse side effects, and enhances functional recovery from acute and chronic pain [60]. Table 3 shows RCTs on APAP for MMA [62–97].

Using the Dixon and Mood up-and-down method, Zeidan *et al.* calculated the median antinoceptive ED_{50} of APAP and morphine given either alone or in combination for postoperative pain in humans. In isobolographic analyses, APAP demonstrated an addictive, opioid-sparing activity with the median ED_{50} of morphine declining from 5 mg when given alone to 2.7 mg when given in association with APAP [62].

The pharmacokinetics of APAP and of the NSAID ibuprofen were unaltered when they were given as a FDC [63]. In a RETRO cohort study conducted on patients prescribed with different combinations of analgesics for acute musculoskeletal pain, a APAP-ibuprofen FDC (500–150 mg) was significantly more effective than other systemic analgesics in preventing persistence of pain [64]. In a double-blind RCT, adult patients with acute pain from a musculoskeletal injury were randomized to receive PO APAP 1 g or ibuprofen 800 mg either alone or in combination. Pain decreased in a similar fashion over the 1-h study period in all treatment groups [65]. Friedman and colleagues randomized to PO APAP 650 mg or to APAP 650 mg-oxycodone 10 mg 159 patients with acute musculoskeletal injury and an inadequate relief after ibuprofen 60 mg (40% of total population) [66]. The APAP-oxycodone combination determined a slightly greater pain relief than APAP alone but with more medication-related adverse events [66]. Gong carried out a double blind, parallel arms RCT on patients with moderate pain for closed limb or trunk injuries; patients received PO either APAP or a combination of APAP 1.000 mg, ibuprofen 400 mg and codeine 60 mg [67]. The combination therapy was not superior to APAP alone in terms of analgesia [67]. Chang randomized 411 patients with lower limb injuries (i.e., sprains, strains, fractures, contusions) to a PO combination therapy with APAP and either ibuprofen 400 mg, oxycodone 5 mg, hydrocodone 5 mg or codeine 30 mg [68]. The pain relief at 1 and 2 h after treatment was not significantly different among different treatment groups [68].

Several reviews and meta-analyses demonstrated that APAP for MMA reduced pain scores and LOS in PACU and H after a variety of surgical procedures; APAP had a higher efficacy when was given at regular scheduled intervals rather than it was prescribed-as-needed (*pro re nata* [PRN]), and when it was given in combination with a NSAIDs or an opioid than when given alone [54–64]. In a RCT on patients undergoing colorectal surgery, Aryaie and colleagues demonstrated that the adding of APAP to standard analgesia significantly reduced postoperative MME from 35,0 ± 33 mg to 21,5 ± 18 mg and the incidence of ileus from 22 to 2% [98]. Dinis randomized 170 women with cesarean delivery to an outpatient combination therapy with APAP and ibuprofen with or without hydrocodone; pain scores 2–4 weeks after cesarean delivery were lower in women receiving non-opioid analgesics [74]. Poljak and Chappelle performed a RETRO chart review on 200 women treated after cesarean delivery with either a scheduled or a PRN combination therapy with APAP and ibuprofen [81]. The scheduled dosing group had a statistically significant decrease in pain intensity and MME [81,82]. Durmus evaluated the effects of preoperative administration of placebo, gabapentin 1200 mg alone, or gabapentin in combination with APAP 20 mg/kg for post abdominal hysterectomy pain; gabapentin alone was superior to placebo and the gabapentin and APAP combination was superior to placebo and to gabapentin alone in terms of pain intensity and MME suggesting an additive interaction [83].

In a RCT, Murata-Ooiwa showed that in TKA patients, even within the context of MMA including periarticular injections of methylprednisolone, ropivacaine, morphine and IV injections of NSAIDs, the adding of IV APAP produced a significant pain relief compared with placebo [76]. In patients undergoing reconstructive pelvic surgery,

Table 3. Analgesic efficacy of paracetamol for multimodal analgesia.

First author, publication year	Population, time to outcome	Study	Patient number, groups	Treatment doses (mg)	Doses/timing	Outcome
Bondarsky, 2013	Acute musculoskeletal pain, 1h	RCT	90, 3	IBU 800/ APAP 1000/ IBU 800-APAP 1000	1	No difference
Chang, 2017	Acute extremity pain, 2h	RCT	411, 4	APAP 1000-IBU 400/ APAP 325-OXY 5/ APAP 300-HYDRO 5/ APAP 300-COD 30	1	No difference
Friedman, 2021	Acute musculoskeletal pain, 2h	RCT	393, 2	APAP650/ OXY10-APAP 650	1	OXY10-APAP650 >APA650: pNRS OXY 10-APAP 650 <APAP 650: AEs
Gong, 2019	Acute musculoskeletal pain. 1h	RCT	118, 2	APAP 1000/ APAP 1000-IBU 400-COD 60	1	No difference
Aweke, 2020	Abdominal surgery, 24h	RCT	63, 3	PreOp PO APAP 1000/ PreOp PO APAP 1000 – IM DICL 75/ PreOP PO APAP 1000 – IV TRAM 100	1	PO APAP- IV TRAM >PO APAP: pNRS, MMEs PO APAP – IM DICL >PO APAP: pNRS. MMEs
Petrikovets, 2019	Pelvic surgery, 24h	RCT	63, 2	PostOp PO APAP 1000- IV TOR 20-IV HYDRO/ PostOp PO APAP 1000 - PO APAP- PO OXY 5/325 IV HYDRO 0,2	Q6H	AC >PRN: pVAS, sVAS
Reagan, 2017	Pelvic surgery, 7 days	RCT	138, 2	UC/ PreOp-PostOp CELEC-GBP IntraOp-PostOP APAP PRN IBU-NARC	–	MMA >UC: MME
Dinis, 2020	Cesarean section, 4 weeks	RCT	170, 2	APAP 325 - 650 - IBU 600/ APAP 325 - HYDRO 5	Q4–6H Q4H	APAP-IBU >APAP-HYDRO: pNRS
Durmus, 2007	Abdominal hysterectomy, 24h	RCT	75, 3	PLACEBO/ GPN 1200/ GPN 1200 – APAP 20 mg/kg		GPN-APAP >GPN >PLACEBO: pVAS, MMEs
Daniels, 2019	Bunionectomy, 48h	RCT	276, 4	PLACEBO/ IBU 300/ APAP 1000/ APAP 1000 – IBU 300	Q6H	APAP 1000 – IBU 300>PLACEBO, IBU 300, APAP 1000: $SPID_{48}$, MMEs
Gupta, 2016	THA-TKA, 5 days	RCT	76, 2	APAP 1000 – IBU 800/ IBU 800	Q6H	APAP 1000 – IBU 800 >IBU 800: pVAS
Murata-Ooiwa, 2017	TKA, 24h	RCT	67, 2	APAP 1000/ PLACEBO	Q6H	APAP >PLACEBO: pVAS
Singh, 2021	RCR, 7 days	RCT	57, 3	PostOp APAP 1000 – OXY 5/ PostOp OXY 5/ PreOp- PostOp APAP 1000 OXY 5	Q6H PRN	Preop-postop APAP >preop APAP: pNRS, MME
Takeda, 2019	THA, 24h	RCT	97, 2	PCA-FENT-PostOp APAP 1000/ PCA-FENT	–	PostOp APAP >PCA-FENT: pNRS

AE: Adverse event; APAP: N-acetyl-para-aminophenol, paracetamol; COD: Codeine; DICL: Diclofenac; FENT: Fentanyl; GPN: Gabapentin; HYDRO: Hydromorphone; IBU: Ibuprofen; IV: Intravenous; MED: Morphine equivalent dosing; MME: Morphine milligram equivalent; OXY: Oxycodone; pNRS: Pain Numerical Rating Scale; PACU: Post-anesthesia care unit; PreOP: Preoperative; PR: Pain relief; PRN: *Pro re nata*; pVAS: Pain Visual Analog Scale; Q2H Q6H Q8H: *Quaque secunda sixta octa hora*, every 2, 6, 8 h; RCR: Rotator cuff repair; RCT: Randomized controlled trial; sVAS: Satisfaction Visual Analogue Scale; $SPID_{24\,48}$: 24–48 h postoperative sum of pain intensity difference; $SPRID_{0–8}$: Sum of pain relief and pain intensity difference scores from 0 to 8 hTHA, total hip arthroplasty; TKA: Total knee arthroplasty; TME: Third molar extraction; TRAM: Tramadol; UC: Usual care; WOMAC: Western Ontario and McMaster University.

Table 3. Analgesic efficacy of paracetamol for multimodal analgesia (cont.).

First author, publication year	Population, time to outcome	Study	Patient number, groups	Treatment doses (mg)	Doses/timing	Outcome
Thybo, 2019	THA, 24h	RCT	556, 4	APAP 1000 – IBU 400/ APAP 1000 – PLACEBO/ IBU 400 – PLACEBO/ APAP 500 – IBU 200	Q6H	APAP 1000 – IBU 400 >APAP 1000: pVAS APAP 1000 – IBU 400 = IBU 400: pVAS
Atkinson, 2015	TME, 24h	RCT	159, 4	PLACEBO/ APAP 250/IBU 75/ APAP 500/IBU 150/ APAP 1000/IBU 300	Q6H	Dose effect: SPID 24
Daniels, 2011	TME, 12h	RCT	669, 5	PLACEBO/ APAP 500/IBU 200/ APAP 500/IBU 400/ APAP 500/COD 15/ IBU 200/COD 12,2	1	APAP 500/IBU 200 highly effective: pVAS
Kellstein and Leyva, 2020	TME, 12h	RCT	394, 5	PLACEBO/ IBU 400/ IBU 200/APAP 500/ IBU 250/APAP 500/ IBU 300/APAP 500	1	IBU/APAP >PLACEBO on $SPRID_{0–8}$ IBU/APAP = IBU on $SPRID_{0–8}$
Mehlisch, 2010	TME, 8h	RCT	678, 8	PLACEBO/ IBU 200/ IBU 400/ APAP 500/ APAP 1000/ IBU 100/APAP 250/ IBU 200/APAP 500/ IBU 400/APAP 1000	1	IBU 200–400/APAP 500–1000 > PLACEBO, IBU, APAP on $SPRID_{0–8}$
Searle, 2020	TME, 12h	RCT	568, 4	PLACEBO/ APAP 650/ IBU 250/ APAP 500 - IBU 250	1	APAP 500-IBU 250 >IBU 250, APAP 650, PLACEBO: pNRS
Pereira, 2017	Keratectomy, 72h	RCT	80	PLACEBO/ APAP 500/COD 30	Q4H	APAP 500/COD 30 >PLACEBO: pNRS
Doherty, 2011	Chronic knee pain, 13 weeks	RCT	892	IBU 400/ APAP 1000/ IBU 200-APAP 500/ IBU 400-APAP 1000	Q8H	IBU 200-APAP 500, IBU 400-APAP 1000 >IBU: WOMAC >APAP: WOMAC
Mullican, 2001	Chronic pain, 4 weeks		462	APAP 300/COD 30/ APAP 325/TRAM 37,5	–	APAP 300/COD 30 = APAP 325/TRAM 37,5: PR

AE: Adverse event; APAP: N-acetyl-para-aminophenol, paracetamol; COD: Codeine; DICL: Diclofenac; FENT: Fentanyl; GPN: Gabapentin; HYDRO: Hydromorphone; IBU: Ibuprofen; IV: Intravenous; MED: Morphine equivalent dosing; MME: Morphine milligram equivalent; OXY: Oxycodone; pNRS: Pain Numerical Rating Scale; PACU: Post-anesthesia care unit; PreOP: Preoperative; PR: Pain relief; PRN: *Pro re nata*; pVAS: Pain Visual Analog Scale; Q2H Q6H Q8H: *Quaque secunda sixta octa hora*, every 2, 6, 8 h; RCR: Rotator cuff repair; RCT: Randomized controlled trial; sVAS: Satisfaction Visual Analogue Scale; $SPID_{24\,48}$: 24–48 h postoperative sum of pain intensity difference; $SPRID_{0–8}$: Sum of pain relief and pain intensity difference scores from 0 to 8 hTHA, total hip arthroplasty; TKA: Total knee arthroplasty; TME: Third molar extraction; TRAM: Tramadol; UC: Usual care; WOMAC: Western Ontario and McMaster University.

a MMA regimen including pre- and postoperative celecoxib and gabapentin, intra- and post-operative IV and PO APAP and ibuprofen, reduced postoperative opioid requirements [69].

In 2010, Mehlisch published a double-blind, parallel group RCT on 750 patients undergoing extraction of three, of which at least two mandibular, impacted third molars; patients had been treated only with placebo, APAP or ibuprofen alone or with different APAP-ibuprofen FDCs [91]. APAP-ibuprofen 500–200 mg and 1000–400 mg were significantly more effective than comparable doses of APAP or ibuprofen alone and more effective than placebo in providing sustained pain relief [91]. Merry and colleagues carried out an RCT on patients undergoing the removal one or more wisdom teeth under general or local anesthesia; patients were instructed to take before and every 6 h for up to 48 h after surgery two tablets each containing either a FDC of APAP-ibuprofen 500–150 mg or APAP 500 mg or of ibuprofen 150 mg; pain intensity was measured up to 48 h after surgery at rest and on activity with a 0–100 mm pVAS [92]. The APAP-ibuprofen combination provided a significantly superior analgesia than APAP or ibuprofen alone [92]. More recently Kellstein and Leyva carried out an RCT on the effects of placebo, APAP and APAP-ibuprofen FDCs (ie, 500–200, 500–250 and 500–300 mg); they found that all APAP-ibuprofen FDCs provided analgesic efficacy that was superior to placebo and comparable to that of ibuprofen 400 mg [93]. Atkinson and colleagues determined the pain relief after oral surgery by a range of APAP-ibuprofen FDCs (i.e., 250–75 mg, 500–150 mg and 1000–300 mg); they found that the analgesic effect of APAP-ibuprofen combination was strictly dose-dependent not only for pain relief but also for response rate, percentage of participants requiring rescue and amount of rescue medications [94]. Discrepancies among studies have been ascribed to different methodologies.

Doherty and colleagues assessed APAP and ibuprofen given alone or in FDC for 13 weeks to 892 patients with chronic osteoarthritis knee pain [95]. At outcome significantly more participants taking one or two FDC tablets rated their treatment as excellent/good compared with APAP [95]. Mullican assessed the effect of APAP-tramadol (325–37.5 mg) and APAP-codeine (300–30 mg) on chronic non-malignant low back pain and osteoarthritis pain [96]. The two combination were similarly and highly effective in attenuating pain intensity [96]. In an RCT, Pereira found that the combination therapy of APAP 500 mg and codeine 30 mg was significantly superior to placebo for pain control after photorefractive keratectomy [97].

Conclusion

Pain and pain disability continue to be a major social issue [1,2]. Although opioid-based treatments remain important for reducing acute pain and preventing pain chronification, side effects limit their dose escalation and efficacy [1,2]. The problem of pain treatment is becoming more difficult to deal with because of the numbers of pain patients are increasing and the development of new non-opioid pain drugs is slow [1–3,98–106]. In the meanwhile, many investigations have been carried out to evaluate alternative strategies of pain control to improve patient's functional recovery and wellbeing by optimizing the available and safest treatments [106].

Tolerability is a key determinant of pain treatment efficacy. As it reduces NSAID and narcotic drug requirements, MMA may benefit all patients with pain. However, MMA is of special interest to those patients who have a reduced tolerability and/or a high risk of opioid adverse events including cognitive impairment and sedation, motor impairment and risk of falls, constipation and urinary retention [3,98–105]. Older adults, comorbid and frail patients are especially susceptible to unwanted side effects of opioids. Furthermore, non-opioid pain therapy has shown to improve mobility and clinical outcome in elderly patients [100]. Finally, as they suffer from unrelieved pain disproportionately more than younger people and are rapidly growing in number due to the aging of the world's population, the elderly patients are those who would benefit most from MMA [3,102–104]. However, the elderly people are under-represented in trials on pain treatments and the evidence on APAP for MMA in aged patients is less than for the young adults [3,99,102]. As a consequence, the profile of efficacy, side effect and tolerability, and the impact of multiple drug therapies on pain medications are largely unknown.

When tested in the geriatric population, however, APAP proved to effectively contribute to MMA [98,100–105]. In a RETRO analysis on 131 elderly patients with fragility hip fractures, the use of regional anesthesia and APAP reduced MMEs [101]. Postoperative administration of APAP significantly reduced the postoperative pain score and MMEs after THA in elderly patients [76]. However, inspite of its analgesic and opioid-sparing properties and of being included in guidelines, APAP is still underutilized in the geriatric population with only a small percentage of elderly patients receiving APAP prior to opioid for control of postoperative pain [6,103,105].

The MMA offers the advantage of reducing the dosages and the side effects of opioids, increasing thus the numbers of patients getting an effective pain control. It can be achieved by combining multiple pain-treatment modalities which exploit the additive or synergistic analgesic activities of different antinociceptive and anti-neuropathic drugs.

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The choice of a specific non-opioid agent to be incorporated into an MMA regimen should be patient-specific and based on patient clinical profile of comorbidities and therapies and on the agent safety and tolerability. APAP is a drug of widespread use worldwide. It has a remarkable safety record and a side effect profile higher than other analgesic drugs. Although its efficacy as a sole analgesic agent is low-to-moderate, APAP consistently enhances the analgesic efficacy of NSAIDs, opioids and anti-neuropathic agents within MMA treatments.

Future perspective

Despite progresses in pain pathophysiology and pharmacology, the relief of pain is still an unmet and growing need because of the partial efficacy of available analgesics and the population aging. Until new, safe, and effective treatments will become available, the efficacy of the current therapeutics should be maximized. Clinical and real-world studies indicate that APAP within MMA improves patient care in different clinical settings. Well-designed, methodologically sound studies are warranted to further support the therapeutic decision making for frail and geriatric patients who are being understudied in spite of being the largest patient population needing an effective pain control.

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