Pain Physician 2021; 24:243-252 • ISSN 1533-3159

Literature Review

Establishment of an Individualized Chronotherapy, Autonomic Nervous System, and Variability-Based Dynamic Platform for Overcoming the Loss of Response to Analgesics

Henny Azmanov, MD[1], Edgar L. Ross, MD[2], and Yaron Ilan, MD[1]

From: [1]Department of Medicine, Hebrew University-Hadassah Medical Center, Jerusalem, Israel; [2]Pain Management Center, Harvard Medical School, Brigham and Women's Hospital, Chestnut Hill, MA, USA

Address Correspondence:
Yaron Ilan, MD
Department of Medicine, Hebrew University-Hadassah Medical Center
PO Box 1200, Ein-Kerem, Jerusalem, Israel 91120
E-mail: ilan@hadassah.org.il

Disclaimer: This work was supported by the Roaman-Epstein Research Foundation.

Conflict of interest: YI is the founder of Oberon Sciences and is a consultant for Teva, ENZO, Protalix, Betalin Therapeutics, Immuron, SciM, Natural Shield, Oberon Sciences, Tiziana Pharma, Plantylight, and Exalenz Bioscience.

Manuscript received: 08-05-2020
Revised manuscript received: 09-12-2020
Accepted for publication: 0-24-2020

Free full manuscript: www.painphysicianjournal.com

Background: Control of chronic pain and mainly the partial or complete loss of response to analgesics is a major unmet need. Multiple mechanisms underline the development of tolerance to analgesics in general and specifically to opioids. The autonomic nervous system (ANS) plays a role in the development of analgesic tolerance and chronobiology.

Objectives: To review the mechanisms associated with the development of nonresponsiveness to analgesics.

Study Design: Literature review.

Setting: The review is followed by a description of a new method for overcoming resistance and improving the response to analgesics.

Methods: Conducted a detailed review of the relevant studies describing the mechanisms that underlie tolerance to pain medications, and the potential roles of the ANS and chronobiology in the development of drug resistance.

Results: The autonomic balance is reflected by heart rate variability, an example of a fundamental variability that characterizes biological systems. Chronotherapy, which is based on the circadian rhythm, can improve the efficacy and reduce the toxicity of chronic medications. In this article, we present the establishment of an individualized variability- and chronobiology-based therapy for overcoming the compensatory mechanisms associated with a loss of response to analgesics. We describe the premise of implementing personalized signatures associated with the ANS, and chronobiology, as well as with the pathophysiology of pain for establishing an adaptive model that could improve the efficacy of opioids, in a highly dynamic system.

Limitations: The studies presented were selected based on their relevance to the subject.

Conclusions: The described variability-based system may ensure prolonged effects of analgesics while reducing the toxicity associated with increasing dosages.

Key words: Painkillers, opioids, drug resistance, compensatory mechanisms

Pain Physician 2021: 24:243-252

Control of chronic pain and mainly the partial or complete loss of response to analgesics is a major unmet need. More than 100 million individuals in the United States experience chronic pain, and approximately one-quarter of them experience daily pain, and 14 million experience severe pain. One-third of the cancer patients on anticancer therapy and approximately half of the patients with an advanced disease experience moderate-to-severe pain (1). Most analgesics have a number needed to treat for 50% pain relief in chronic pain of between 3 and 10, and the superior effect of the primary drug over placebo is approximately 30% (2).

Opioids administered by various routes are the mainstay of severe pain management (3-5). Prescribing strong opioids in patients with chronic pain requires precision in management. Both genetic and epigenetic factors contribute to the development of drug resistance in patients with chronic pain (6,7). Genetic variation in receptors contributes to the various responses to opioids within or between individuals (8). Individual parameters including the source of the pain, age, gender, analgesics including opioids, pharmacokinetics and pharmacodynamics, genetic polymorphism, physiology, comorbidities, environmental factors, medication interference, and treatment adherence are all associated with the degree of efficacy and the gradual loss of response (9). A patient's prior exposure to opioids, current medications that interact with or augment the effect of an opioid, and end-organ function are relevant to the outcome of the therapy(10,11).

Data on the role of the autonomic nervous system (ANS) and its effect on rhythmic patterns of pain provide new options for improving the clinical efficacy of current medications and maneuvers for pain control (12).

Methods

In this article, we review some of the data on the use of ANS-based and chronopharmacologic approaches for the treatment of pain and describe the establishment of a new dynamic individualized platform based on both chronotherapy and variability for overcoming the loss of response to analgesics.

Results

Mechanisms of the Loss of Response to Analgesics: Development of Tolerance to Analgesics

Drug tolerance is defined as a decrease in pharmacologic response following repeated or prolonged drug administration. Long-term opioid administration eventually results in a dose ceiling attributable to the rapid onset of analgesic tolerance coupled with a slow development of tolerance and the development of adverse effects including respiratory depression, nausea, and decreased gastrointestinal motility, while the need for effective long-term analgesia remains (13). Tolerance is divided into innate or acquired (13). Innate tolerance is a predisposition to display drug sensitivity or insensitivity owing to pharmacogenetic parameters. It is commonly determined on the administration of the initial dose. Acquired tolerance is attributed to repeated drug exposure and manifests in a long-term decrease in drug response despite constant systemic exposure.

Both the duration and dose of opioid treatment determine the development of tolerance; continuous infusions induce tolerance faster than does intermittent therapy (13). Alterations in opioid receptor interactions with endogenous or exogenous opioids contribute to an overall "opioid tone," which depends on receptor subtype and density. This may be a result of analgesic (e.g., endogenous analgesia), placebo, or hyperalgesia or withdrawal pain effects (14-17).

Acquired tolerance is subdivided into 3 types based on the mechanism (13): pharmacokinetic tolerance develops when drug disposition or metabolism is altered as a function of time; as a consequence of the drug being an inducer or inhibitor of a specific enzyme or transporter system; or because of a time-dependent decrease in the presentation of the active moiety to the receptor. It is associated with the amount of metabolite production, metabolizing enzyme expression, and transporter function (13). Behavioral tolerance develops when an individual learns to function despite repeated exposure to a drug. Conditioned tolerance follows Pavlovian principles in which situational cues are associated with drug administration (18).

Most clinically used opioids act through mu-opioid receptors, which transmit downstream signals through heterotrimeric $G\alpha\beta\gamma$-proteins. Receptor desensitization occurs (19). Opioid metabolism results in metabolites that enhance or antagonize the analgesic effect. Normorphine, the metabolite of morphine, is inactive, whereas morphine-6-glucuronide metabolites are more potent compared with morphine, and the morphine-3-glucuronide metabolite has hyperalgesic effects that oppose the analgesic effects of morphine (20). A contributor to morphine tolerance is the slow recovery of a desensitized G protein-coupled receptor kinase–mediated phosphorylation (21). An altered opioidergic tone is documented in patients with specific single-nucleotide polymorphism opioid profiles and pain susceptibility (22) and with increased sensitivity to methadone and in heroin addicts.

Analgesic use contributes to pain chronification (23). Long-term opioid use leads to exaggerated opioid tolerance, characterized by escalating dose requirements to maintain analgesia, and contributes to opioid-induced hyperalgesia (13,24). One method commonly used in patients who develop resistance is increasing their dosages. The recommendation is that if a single

dose of an immediate-release opioid provides no pain relief and causes no side effects, then the dose may be increased (25). An extended-release opioid was recommended for patients with inadequate pain control with PRN use or who required 4 or more PRN doses per day regularly to control pain and maintain functional status (10). However, these measures may further augment the vicious cycle of inducing resistance.

In chronic pain characterized as "opioid-induced hyperalgesia," the opioid itself contributes to or is part of chronification. A similar pattern of pain exacerbation is observed in patients with chronic methadone use who also show increased sensitivity to experimental and clinical pain (26). Functional magnetic resonance imaging of the brain showed opioid-induced changes in regions implicated in the regulation of affect and impulse control, and in reward and motivational functions (27). Alterations of these functions characterize chronic pain, implying that a cross-sensitization process may occur whereby opioids enhance the derangement of the brain structure and functional circuits (14,28,29). Opioid hyperalgesia is dose related, but also related to preexisting personality types as seen with certain psychological conditions such as anxiety.

Systemic inflammatory responses in patients in the intensive care unit are mediated by the release of proinflammatory substances and activation of spinal cord N-methyl-D-aspartate receptors. Activation of endogenous antinociceptive mechanisms and the inhibitory opioidergic, serotonergic, and noradrenergic pathways in the brain reduces nociception (24). Long-term administration of oxycodone, morphine, and alfentanil upregulates P-glycoprotein expression in the brain capillaries and leads to increased efflux and reduced drug penetration to the central nervous system (CNS). A similar effect was described for TNF alpha. Inflammation increases alpha-1 glycoprotein, which binds methadone and leads to a lower concentration of free methadone in the plasma (30). Cytokine release from activated immune cells leads to exaggerated nociception (31). Endogenous opioid peptides are released by leukocytes at the injury site and interact with the injury-induced opioid receptors that are upregulated along nerve terminals to reduce pain (32).

Chronic use of morphine leads to a change in the composition of the microbiome. The process of bacterial translocation in the gastrointestinal tract is associated with activation of epithelial Toll-like receptors and on enteric glia by the bacterial pathogens such as lipopolysaccharides. These activated glia release proinflammatory cytokines, which decrease the response to analgesics. Treatment with antibiotics, particularly oral vancomycin, reduced the number of bacteria, thereby decreasing the changes caused by morphine use (33,34).

The multiple mechanisms associated with the development of analgesic tolerance and resistance, along with marked intra- and interpatient differences in responses under different settings, makes this highly dynamic system a major challenge to overcome.

The Circadian Rhythm Underlies the Machinery of Chronic Pain

Biological rhythms are characterized by the circadian clock around the geophysical time close to 24 hours. The circadian rhythm is regulated by the hypothalamic suprachiasmatic nucleus in the brain, which functions as a core pacemaker and drives the transmission of oscillation signals that are spread across peripheral tissues via humoral and neural connections. Intracellular clocks are regulated by transcriptional/translational feedback loops, which generate molecular oscillations. The synchronization between the central brain oscillator and tissue-specific oscillators provide the homeostasis required for organ functions (35).

Chronobiology describes cyclic behaviors in biological systems (36). Circadian rhythms control the timing and quantity of the secretion of hormones and neurotransmitters. An imbalance of the circadian rhythm leads to the production of hormones and neurotransmitters in aberrant amounts or at incorrect times (37). The circadian rhythm plays a role in the mechanisms of chronic pain, including headache and neuropathic pain (38). Circadian changes were involved in nociception (39). Patients with chronic pain report exacerbation of pain at specific times of the day, attributed to a temporal variation of the body's inhibitory pain response (40). Circadian pain patterns characterize various nociceptive pain conditions, such as arthritis, and neuropathic pain, in which degree of pain fluctuates based on a distinct diurnal rhythm that contrasts that of nociceptive pain conditions (41). Circadian rhythmicity characterizes inflammatory pain, and the diurnal pattern was documented for peripheral neuropathies and for cluster headache. The cranial autonomic symptoms in cluster headache are generated by a central pacemaker without activation of the peripheral trigeminovascular network (42). Both preclinical and human data for fibromyalgia showed associations between the physiology of the sleeping-waking brain and musculoskeletal pain and chronic fatigue (43). Small fiber neuropathy is

associated with pain that has only a moderate response to standard regimens of treatment. An inverse relationship with the quality of sleep and pain intensity was also shown (44). Insomnia is prevalent in patients with chronic pain and is associated with a lack of response to treatments (45).

The circadian rhythm regulates the central and peripheral nervous systems and the function of immune cells associated with pain. Neuroinflammation mediated by monocytes, T and B lymphocytes, neutrophils, and microglia in the CNS plays a role in neuropathic pain. The pain signals are transmitted via sensory neurons in the peripheral nervous system, expressing receptors and channels that respond to mediators secreted from inflammatory cells (46). Timing with meals, satiety (47), circadian hormonal changes (48-52), and function of liver enzymes (53) may also be associated with circadian changes.

These findings support a role for chronobiology in the mechanism of pain.

Use of Chronotherapy for Improving the Efficacy and Reducing the Toxicity of Analgesics

The circadian rhythm is associated with alterations in both the availability and function of receptors, hormones, and other compounds, which affect the pharmacokinetics and pharmacodynamics of drugs. Chronotherapy is based on the administration of medications according to the circadian rhythm at a specific time of the day to achieve adequate serum concentrations and the maximal therapeutic effect and to reduce toxicity (35). Genome-wide association studies that integrated the pharmacokinetics and pharmacodynamic processes of drug reactions led to development of chronopharmacodynamics concepts showing that alterations in timing and rate of drug administration are associated with the drug response. The concept of heterochronopharmacodynamics describes the impact of genes on drug efficacy and drug toxicity based on the circadian rhythm of the body in association with alterations in drug concentrations (54). There seems to be a time-dependent release of endogenous opioid peptides such as bradykinin, substance *P*, glutamate, nitric oxide, interleukin1 (IL), IL6, and 5-hydroxytryptamine (12).

The circadian rhythm controls the response to analgesics. Neuropathic pain is worse at night. Diurnal variations in pain intensity before and during analgesic treatment were assessed in patients with diabetic neuropathy and postherpetic neuralgia. Data from untreated patients showed an effect of time of day but no effect of day of the week. Pain intensity progressively upsurges throughout the day and this pattern was maintained during treatment with gabapentin and morphine. Circadian variation also impacts labor pain (55).

Circadian release of intrinsic hormones including cortisol, melatonin, and endogenous opioid peptides such as metaenkephalin and β-endorphins affects both the dose and frequency of analgesics based on μ-receptor agonists (56,57). Melatonin is an endogenous neurohormone that contributes to circadian rhythms. Cortisol peaks around 6 am, whereas melatonin exerts its effect at night. The secretion of bradykinin, 5-hydroxytryptamine, glutamate, nitric oxide, substance P, and several cytokines is time-related (58). Downregulation of opioid receptors during the morning, early afternoon, and late evening hours has been documented in preclinical studies. Respiratory depression by therapeutic doses of opioids is more common in the afternoon, a time during which the opioid receptors are downregulated. Administration of melatonin exerts analgesic and neuroprotective effects in chronic pain (37). Melatonin mediates nocturnal pain in patients with a rotator cuff tear or frozen shoulder. The expression of melatonin receptor 1A and 1B and of acid-sensing ion channel 3 (ASIC3) in the subacromial bursa and the joint capsule increased in patients with a rotator cuff tear and frozen shoulder. Melatonin treatment induced ASIC3 expression and IL-6 production, and administration of a melatonin-receptor antagonist reversed melatonin-stimulated ASIC3 expression and IL-6 production, supporting the effect of the circadian rhythm on the development of pain and response to therapy (59).

Studies show circadian variations in beta-endorphin levels higher in the early morning and lower in the afternoon, this correlates with levels of melatonin (60,61). Several animal studies show that melatonin mediates the release of beta-endorphins (62,63).

Current guidelines recommend the use of analgesics "by the clock" rather than "on demand." However, administration of analgesics over constant or continuous regimens ignores the time fluctuations in pain perception and the effect of chronotherapy on the pharmacokinetics and pharmacodynamics of analgesics (64). Strategies for mitigating opioid tolerance include altering the times of administration and reducing the dose and the duration of treatment (24,65). Improving drug efficacy by using rhythm-based regimens and clock-modulating compounds was suggested to improve efficacy and reduce the toxicity of pain medications (66).

Scheduling of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) based on the circadian hormonal profile showed improved therapeutic effects and reduced toxicity (57). Administration of opioids in the evening is more effective compared with that during the early morning (67). Improved absorption, more protein binding, which decreases renal toxicity, and more opioid-sparing were observed after morning administration of oral NSAIDs (57). A drug formulation intended to have a predetermined lag time of 6 hours prior to release was developed to target the circadian rhythms of rheumatoid arthritis (68).

Interrupted infusions of analgesics were shown to improve the clinical effect while reducing side effects and enabled more awake time (69). Conversion to intermittent bolus therapy or patient-controlled analgesia was recommended to patients from the beginning of therapy (70). It was suggested that chronification can be reversed with drug withdrawal or decreased dosing (71). Drug holidays are used for chronic opioids as a means for overcoming tolerance (72). In a retrospective investigation, the long-term effects of continuous intrathecal opioid therapy via implantable infusion pump systems were examined in 120 patients with chronic pain. In a long-term observational study of patients who received intrathecal morphine for longer than 4 years, 64% had a constant dosage history, 35% required an increased morphine dosage within 1 year, and 25% developed tolerance, in half of whom tolerance was controlled by means of "drug holidays" (73).

Tramadol provides analgesia by its dual mechanism of action, opioid and monoaminergic. Its major metabolite O-desmethyltramadol (M1) has a weak affinity at μ-opioid receptors as an agonist. The monoaminergic activity is mediated by the 2 stereoisomers of tramadol itself, which act synergistically on serotonergic and noradrenergic mechanisms of pain transmission (74). In a trial conducted in 18 volunteers, the bioavailability of once-daily extended-release tramadol was not affected by the time of administration. Total and maximum exposure of the product was bioequivalent after intake in the morning and at night. Maximum exposure of tramadol (geometric means of C(max) values) was similar after morning or evening administration. The extent of tramadol exposure and Tmax values were also comparable (75). Although the exact mechanism for the noted loss of response is to be determined, these results suggest that the clinical effect of circadian rhythm–based regimens cannot be attributed solely to the effects on drug distribution. The marked intra- and interpatient variability when applying chronotherapy for the treatment of chronic pain suggests that individual parameters play a role in both the periodicity of the mechanism of pain and in the development of resistance to drugs. Treatment programs need to be individualized to the patient's circadian rhythms, type of pain, and response to analgesics (64). The continuously dynamic patterns of these changes imply the need for flexible regimens to improve the results (64).

Taken together, these results support the implementation of chronotherapies for improving responses to analgesics.

The ANS Underlies the Machinery of Chronic Pain and Response to Analgesics

The ANS is important for both determining the efficacy and development of resistance to analgesics. Both the sympathetic and parasympathetic nervous systems regulate the development of pain and malfunction during chronic pain. Several receptors take part in nociceptin in the dorsal horn, such as alpha-2-adrenoreceptors, tachykinin, opioid, and glutamate receptors. Activation of the hypothalamic-pituitary-adrenal axis inhibits the development of morphine tolerance. Daily co-administration of either alpha- or beta-adrenergic blockers with morphine suppressed the development of tolerance to morphine without impairing the analgesic effect. Co-administration of both blockers with morphine maintained the analgesic effect; however, when the administration of either one or both blockers was eliminated, tolerance developed (76). Inhibition of analgesic tolerance to morphine by epinephrine was shown in an animal model of pain (77). Alpha 2-adrenoceptor agonists prolong opioid analgesia while attenuating the development of tolerance. Ultra-low doses of nonselective alpha 2-adrenoceptor antagonists augment acute spinal morphine antinociception and block morphine tolerance (78). In a rat model, the co-injection of alpha 2-adrenoceptor agonists with morphine attenuated tolerance (79). Low doses of competitive alpha 2-adrenoceptor antagonists can augment acute morphine analgesia and block or reverse tolerance to spinal administration of morphine (80). Overall these data support the ability to use the ANS for improving drug efficacy.

This disruption in the autonomic balance is reflected by heart rate variability (HRV) (81). HRV also reflects the circadian rhythm and is associated with chronotherapy. It can serve as a prognostic marker for cardiac and noncardiac chronic diseases. Chronic pain is mediated

by reduced parasympathetic activity, which is reflected by a low HRV (82). A review of 51 studies evaluating HRV in chronic pain suggested a decrease in the high-frequency parameter of HRV in chronic pain, implying a decrease in parasympathetic activation (83). In a review of 20 trials, an increase in sympathetic-baroreflex activity and a decrease in vagal-parasympathetic activity, as reflected by changes in frequency domain measures of HRV, correlated with pain (84).

Irregularities in HRV, reflective of ANS activity, are associated with pain sensitivity, chronic pain, and pain modulatory mechanisms (85). HRV indices were associated with pain intensity in patients with chronic neck pain (86). Patients with spinal cord injury and chronic neuropathic pain showed a lower overall HRV (87). Chronic pain is associated with a disturbance of the vagus nerve descendent inhibitory pathway, which can be assessed by HRV measurements (88). A study of patients who maintained a cancer breakthrough pain log showed that low frequency/high frequency may be a useful surrogate marker for pain alleviation (89). Preoperative HRV predicted patients' pain, enabling those with a higher predicted score to have surgery under general anesthesia (90). Various chronic pain conditions are characterized by a lack of endogenous pain modulation and reduced resting HRV. In a study of 63 healthy individuals, resting HRV was associated with endogenous pain modulation (91). In a study of healthy male volunteers, propranolol increased HRV but did not affect pain sensitivity. Although this may suggest that the increased HRV from propranolol is not associated with peripheral and central pain pathways in healthy male patients, it also implies that interindividual variability may underlie the discrepancies (85). These data support the role of the ANS in the pathogenesis of pain and in the response to therapy and imply that ANS-associated measures, such as HRV, can be used for assessing the degree of severity of chronic pain and for the development of therapeutic regimens.

Discussion

Establishing a Dynamic Algorithm Based on Individualized Variability, ANS, and Chronobiology for Overcoming the Compensatory Mechanisms Associated with Loss of Response to Analgesics

Improving the long-term effects of painkillers while reducing their toxicity is based on considering the following 3 concepts in a distinct dosing regimen: the effect of chronobiology on the mechanism of pain and of chronotherapy on the response to pain; the impact of signatures of the variability of pain-related parameters; and implementing individualization of both.

The platform for the prevention of the loss of response to analgesics is established in 3 stages. In the first stage, the concepts of variability are implemented in analgesic therapy. Variability characterizes normal organization and function of biological systems, from the cellular to whole organ levels (92-96). Loss of normal variability is associated with disease states and poor prognoses (97,98). For the treatment of pain, randomness in dosing and time of administration are implemented to prevent tolerance to painkillers. This stage enables overcoming tolerance in a nonchronotropic and nonindividualized way (99-103).

In the second stage, individualized chronobiology timings and individualized patterns of variability are added into the algorithm. As some mechanisms of pain are associated with the ANS and both chronobiology and HRV are affected by the ANS, HRV-derived parameters serve as one of the pain-related parameters incorporated into the platform. Intra- and interindividual patterns of variability including signatures of pain sensitivity, response to therapy, and measures of autonomic activity, are continuously updated in the machine-learning algorithm (84).

In the third stage, variability-based signatures of pain-associated parameters are implemented. These include solid signatures such as genotypes and continuously dynamic signatures including immune signatures, which correlate with the development of chronic pain or the response to analgesics. Quantifying and individualizing these signatures on a continuous basis is being analyzed for assessment of the effect of therapy in a closed-loop learning method. Both the degree of pain and measure of toxicity are used as endpoints for the algorithm, which continuously tailor the therapeutic regimens based on these inputs.

Ongoing clinical trials (NCT03843697; NCT03747705) are evaluating the effects of these regimens in patients with inflammatory bowel disease who have lost their response to anti-TNFs, and in patients with epilepsy who have lost response to antiepileptics. Data from these studies are expected to find improved response to medications when applying variability-based therapeutic regimens (103). Future studies will assess the clinical benefits of using these algorithms in patients with chronic pain.

Figure 1 shows a gradual consistent improvement in efficacy and overcoming of tolerance, which is expected from the implementation of these algorithms.

Conclusion

In summary, ensuring a long-term effect of analgesics while reducing the toxicity associated with an increase is dosages requires the adaptation of new therapeutic regimens while using existing medications. An individualized platform comprising both chronotherapy and variability signatures, which are associated with the mechanism of the pain and with the response to the therapy, was established for overcoming the deleterious effects of the compensatory mechanisms associated with the development of the loss of response to analgesics. The ongoing trials implementing this platform will enable fine-tuning of the algorithm for ensuring long-term improved efficacy and reduced toxicity of opioids.

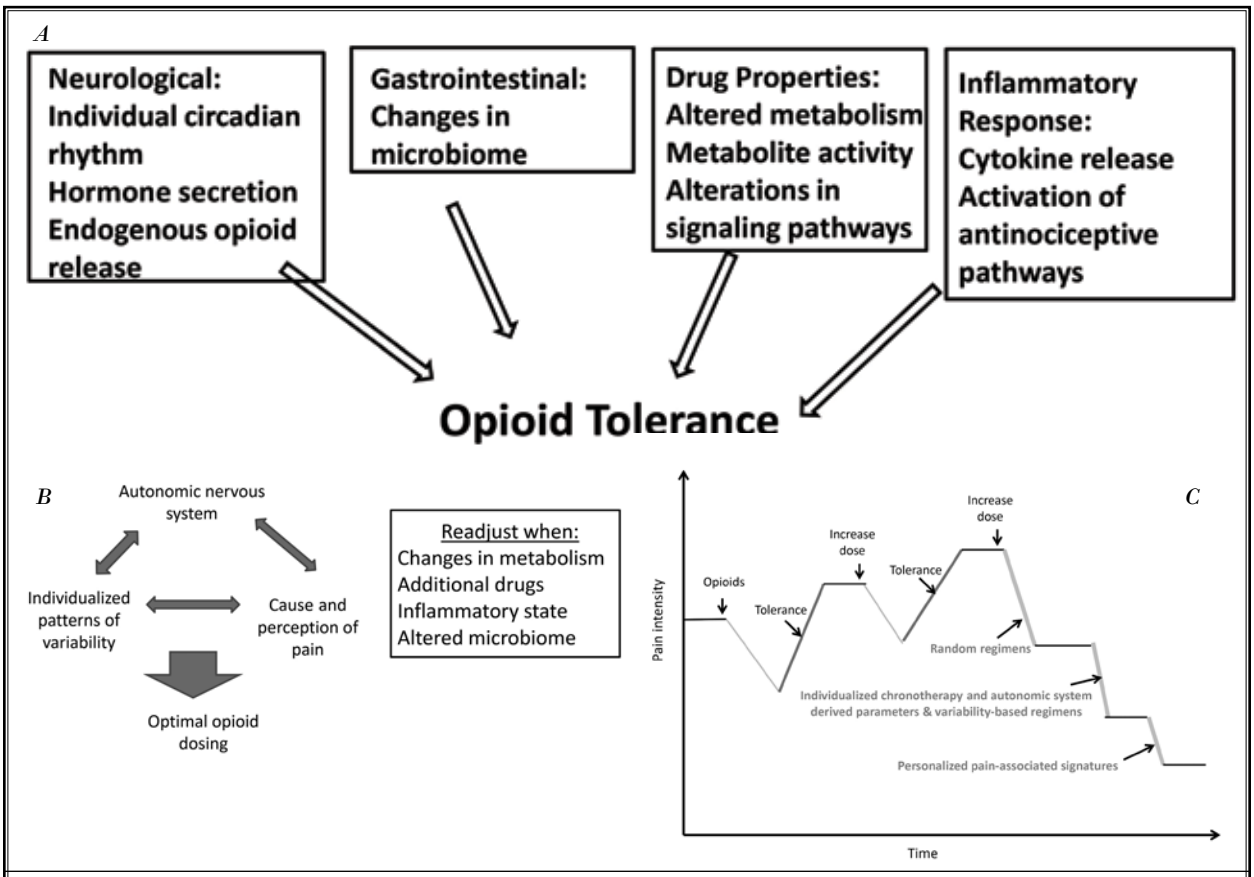

Fig. 1. *(A) Several mechanisms that lead to the development of opioid tolerance. (B) A schematic representation of the approach for establishing an individualized therapy based on the ANS, variability, and chronobiology for overcoming the compensatory mechanisms associated with the loss of response to analgesics. (C) A machine-learning closed-loop algorithm is used for implementing the chronobiology- and ANS-associated parameters, variability measures, and other pain-related signatures (e.g., genotype and immune signatures), in a continuous manner, for improving the response and reducing the toxicity of opioids.*

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