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Drugs used in the treatment of opioid tolerance and physical dependence: a review.

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Abstract

Opioid drugs used in the treatment of severe pain are known to produce tolerance that requires a dose increase to maintain a sufficient analgesic effect. As this is connected with side effects such as respiratory depression, it is highly desirable to avoid or at least attenuate the development of tolerance. Closely related, but in some respect dissociable, is the phenomenon of physical dependence, which becomes apparent particularly in heroin withdrawal. Our knowledge about the mechanisms underlying tolerance has increased dramatically in recent years, but a final picture of the importance of each particular mechanism under in vivo conditions has not yet emerged. Recent studies suggest that the so-called receptor down-regulation is not the main mechanism in vivo. A desensitization on the basis of receptor decoupling, receptor internalization and increased alternative coupling to stimulatory G-proteins have been demonstrated. However, a functional antagonism of the opioid effects seems to be clinically most important, mediated by the activation of NMDA receptors, up-regulation of adenylyl cyclase and nitric oxide synthase. Drugs blocking these mechanisms are the most promising option in the treatment of tolerance. Namely, alpha2-adrenoreceptor agonists such as clonidine and NMDA antagonists such as ketamine or dextromethorphan have been used to minimize tolerance development during opioid treatment. Moreover, clinical strategies such as opioid rotation and multimodal analgesia, i.e. the simultaneous application of several analgetics of different type, have proven to be successful approaches.

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