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Mitigating adverse side effects of clinically used mu opioids by targeting exon 7-associated splice variants of the mu opioid receptor gene, *Oprm1*, without altering mu opioid analgesia in pain management

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The single-copy gene (*OPRM1*) encoding the mu opioid receptor (MOR) undergoes extensive alternative splicing, generating multiple splice variants. One set of *OPRM1* variants, exon 7-associated full-length 7-transmembrane (7TM) C-terminal variants (E7 variants), contain a unique intracellular C-terminal tail with 30 amino acids encoded by E7 that are conserved from rodents to humans. E7 variants are abundantly expressed in the central nervous system with distinct distributions. Accumulating evidence has indicated that E7 variants contribute to several mu opioid-induced adverse side-effects. Truncating E7-encoded C-terminal tails in mice (mE7M-B6) attenuated morphine tolerance and reward without effect on analgesia. An antisense oligonucleotide (ASO) targeting E7 variants also reduced morphine tolerance. These observations suggest that *Oprm1* E7 variants mediate several adverse effects associated with clinically used mu opioids, and targeting E7 variants can diminish mu opioid-induced adverse effects but maintain mu opioid analgesic potency via other *Oprm1* 7TM variants. The current studies further establish the role of E7 variants in mediating mu opioid-induced tolerance, reward, and respiratory depression in mE7M-B6 or naïve mice by using the ASO and a newly developed rabbit monoclonal antibody (RabmAb) that target E7 variants. Both the ASO and RabmAb attenuated morphine tolerance and reward in mice. Additionally, a new mouse model (mMOR-1O-KI) in which only a single E7 variant, mMOR-1O, is expressed showed enhanced morphine tolerance and reward, complementing the results from mE7M-B6 mice. Together, these studies indicate that E7 variants represent novel therapeutic targets for mitigating adverse effects of clinically used mu opioids without altering analgesia in pain management.