an effective therapeutic target in cetuximab-resistant colorectal cancer. *Cancer Discov* 2011;**1:**508–23.
3 Leto SM, Sassi F, Catalano I, Torri V, Migliardi G, Zanella ER, *et al.* Sustained inhibition of HER3 and EGFR is necessary to induce regression of HER2-amplified gastrointestinal carcinomas. *Clin Cancer Res* 2015;**21:**5519–31.
4 Valtorta E, Martino C, Sartore-Bianchi A, Penaullt-Llorca F, Viale G, Risio M, *et al.* Assessment of a HER2 scoring system for colorectal cancer: Results from a validation study. *Mod Pathol* 2015;**28:**1481–91.
5 Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, *et al.* American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol* 2013;**31:**3997–4013.
6 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, *et al.* ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. *Lancet* 2010;**376:**687–97.
7 Clark JW, Niedzwiecki D, Hollis D, Mayer R. Phase II trial of 5-fluorouracil (5-FU), leucovorin (LV), oxaliplatin (Ox), and trastuzumab (T) for patients with metastatic colorectal cancer (CRC) refractory to initial therapy. *Proc Am Soc Clin Oncol* 2003;**22** (Suppl):Abstract 3584.
8 Ramanathan RK, Hwang JJ, Zamboni WC, Sinicrope FA, Safran H, Wong MK, *et al.* Low overexpression of HER-2/neu in advanced colorectal cancer limits the usefulness of trastuzumab (Herceptin) and irinotecan as therapy. A phase II trial. *Cancer Invest* 2004;**22:**858–65.
9 National Cancer Registry Programme NCRP (2013). *Three-year report of the population based cancer registries 2009–2011.* Bengaluru:National Cancer Registry Programme, Indian Council of Medical Research (ICMR); 2013.

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Medical marijuana laws and marijuana use in the USA: Any lessons?

SUMMARY

Since the mid-2000s, there has been an increase in marijuana use amongst adolescents in the USA. Such use has been reported to be associated with impairment in memory, coordination and judgement in the short term and cognitive impairment, unemployment, psychiatric symptoms and substance addiction in the long term. It has been widely debated that legalization of marijuana use for medical purposes is one of the key reasons for increased marijuana use among adolescents. Since 1996, medical marijuana law has been passed by 23 states of the USA. It is feared that such laws may convey a message that marijuana use is acceptable, thus leading to an increase in its prevalence.

This study addressed two questions: first, whether adolescents were generally at a higher risk for marijuana use in states that ever passed a medical marijuana law by 2014 than adolescents in other states and second, whether adolescents in states that had passed medical marijuana laws were at a higher risk of marijuana use in the years immediately after the passage of the law than adolescents in those states before the passage of the law. The data were taken from the 'Monitoring the Future' study.[1] More than one million (1 098 270) adolescents were recruited in repeated cross-sectional surveys from 1991 to 2014 using a multistage, random sampling design with replacement. The various stages included schools within selected geographical areas (with probability proportionate to school size), and students within school. Up to 350 students per grade from VIII, X and XII grades were recruited. Students randomly selected within the schools, from over 400 schools in 48 contiguous US states (23 of which had passed medical marijuana laws) were asked to fill up self-administered questionnaires (containing questions on drug behaviour, attitude and related factors, background variables, and school experiences, role behaviour and satisfactions) in classrooms or larger group administrations using standardized procedures to maintain confidentiality. Primary outcome was taken as any 'marijuana use within previous 30 days'. Main exposure was 'state level medical marijuana laws'. Multilevel logistic regression modelling of adolescents nested within states was done by calculating adjusted odds ratio and prevalence. Further, a sensitivity analysis was done at various levels, such as fitting the multilevel model 48 times, replacing binary variables with ordered variables, using time varying variable, etc., which made the study more robust. The response rate of students was 81%–91%.

Twenty-one states had passed the medical marijuana law by 2014. The prevalence of marijuana use amongst adolescents in the previous 30 days was higher in the states that had passed such a law (adjusted prevalence 15.87% *v.* 13.27%; adjusted odds ratio 1.27, 95% CI 1.07–1.51; p=0.0057). However, further analysis revealed that states with a medical marijuana law had an increased prevalence of marijuana use even before the law was passed. Overall, the effect of medical marijuana laws on risk of marijuana use among adolescents before versus after passage of the law was not significantly different (adjusted prevalence 16.25% *v.* 15.45%; adjusted odds ratio 0.92, 95% CI 0.82–1.04; p=0.185). Sensitivity analysis did not affect the results. However, there was an unexpected finding that marijuana use was significantly reduced in VIII graders unlike X and XII graders after passage of the medical marijuana law. The authors attributed this to the possibility of more modifiable attitudes towards marijuana as well as more parental check against use in youngest adolescents after passage of the law. However, the authors did not examine additional variations in state medical laws (e.g. approved illnesses, amount of

marijuana permitted) and studied only laws governing medical use of marijuana. The adolescents who were not attending school or were absent were not included. Self-reporting of marijuana use could have led to minimization of reporting despite reassurance about confidentiality.

The study concluded that there was no evidence for an increase in marijuana use among adolescents after passage of medical marijuana laws. However, questions such as, whether marijuana laws increase availability or change adolescent approval for marijuana, remain unanswered. In view of the potential harm from early use, resources should be used to identify the risk factors.

COMMENT

The marijuana (cannabis) plant contains chemicals, called cannabinoids such as tetrahydrocannabinol (THC), cannabigerol (CBG), cannabinol (CBN), and cannabidiol (CBD). Of these, THC is the most psychoactive. It has been reported that these may help treat a range of illnesses or symptoms. The term medical marijuana has been given to different forms of marijuana which are used medically and may be either natural plant products or mixtures of THC and CBD produced in the laboratory. Synthetic cannabinoids such as dronabinol and nabilone have been approved by the US Food and Drug Administration (FDA) and contain cannabinoid chemicals in pill form for treatment of nausea and vomiting associated with cancer chemotherapy and appetite stimulation in patients with wasting diseases such as AIDS.[2] THC and CBD have been found to be more effective than placebo in neuropathic pain.[3] Few other conditions where medical marijuana has been reported to be useful include spasticity and neuropathic pain of multiple sclerosis, fibromyalgia and rheumatoid arthritis.[2]

Marijuana was first classified as a Schedule I substance (high potential for abuse) in the Controlled Substances Act of 1970 and criminalized by the Reagan administration's War On Drugs in the 1980s. It is argued that cannabis use should be legal for medical purposes. Medical marijuana laws are defined as laws that allow an individual to defend himself or herself against criminal charges of marijuana possession if the defendant can prove a medical need for marijuana under state law.[4] The legalization of marijuana has been changing and got approval for medical use, first by California in 1996.[5] After that many states in the USA have approved marijuana for medical purposes. However, the laws vary from state to state in terms of variability in the number of approved medical conditions to variability in the context under which possession, cultivation and use is deemed legal. While some states in the USA indicate medical marijuana for huge number of medical conditions (up to 40 in Illinois), states such as Washington DC have stayed restrictive to up to six conditions requiring

medical marijuana. The US FDA has not recognized or approved the marijuana plant as medicine.

The recreational and medical use of marijuana has been known since ages. In India, it has been used for religious as well as medical purposes since 1000 BC. All forms of cannabis were banned and their possession deemed unlawful as per the Narcotic Drugs and Psychotropic Substances Act, 1985.[6] Thus, historically, the legal status of marijuana has varied from being used for religious purposes, then being banned and again being considered for legalization after passage of medical marijuana laws in various countries. According to the National Household Survey (NHS) conducted in India from March 2000 to November 2001, the prevalence of cannabis use was 3%.[7] It is difficult to comment on the current trend of cannabis use as no other national survey is available on substance use from India after the NHS. However, data from the World Drug 2015 report shows that cannabis use has continued to rise in most regions of the world.

This study suggests that the passage of medical marijuana laws may not be associated with a significant increase in the prevalence of recreational marijuana use among adolescents. The risk of abuse, however, remains an issue where it has been legalized and may even impact the youth of the countries which are yet to legalize marijuana for medical use, such as India. Before legalizing marijuana use, measures must be kept in place to control misuse of such laws and prevent the dispensing units to become reservoirs of illicit marijuana.

REFERENCES

1 Monitoring the future. Available at *www.monitoringthefuture.org/* (accessed on 7 Mar 2016).
2 Kashyap S, Kashyap K. Medical marijuana: A panacea or scourge. *Lung India* 2014;**31:**145–8.
3 Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, *et al.* Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1' studies. *Anaesthesia* 2004;**59:**440–52.
4 Marijuana Resource Center. Available at *www.whitehouse.gov/ondcp/marijuanainfo* (accessed on 7 Mar 2016).
5 Bestrashniy J, Winters KC. Variability in medical marijuana laws in the United States. *Psychol Addict Behav* 2015;**29:**639–42.
6 The Narcotic Drugs and Psychotropic Substances Act, 1985. Available at *http:// cbn.nic.in/html/ndpsact1985.pdf* (accessed on 8 Mar 2016).
7 Ray R. *The extent, pattern and trends of drug abuse in India.* National Survey, Ministry of Social Justice and Empowerment, Government of India and United Nations Office on Drugs and Crime, Regional Office for South Asia. 2004.

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