

FDA APPROVES NUSIRENSEN FOR SPINOMUSCULAR ATROPHY

A fascinating new genre of drugs – Antisense oligonucleotides – is being developed for what were considered incurable diseases. The US Food and Drug Administration (FDA) has now approved Spinraza (nusinersen) for treatment of Spinomuscular atrophy (SMA). The mechanism of action of this drug is worth understanding. The defect in SMA is due to a mutation in the *SMN1* gene. In humans, there exists an alternative gene called the *SMN2*. This encodes a nearly identical protein which differs from *SMN1* by 11 nucleotides. However, due to a single difference in exon-7 of *SMN2* gene, there is altered RNA-splicing of this transcript. The protein produced by this gene rapidly degenerates.

In 2003, Adrian Krainer, a biochemist at the Cold Spring Harbor Laboratory in New York, developed antisense oligonucleotides (ASO), which is a short length of nucleotides which could bind to the pre mRNA produced by the *SMN2* gene. This prevents splicing out of the exon-7. Hence a more stable protein is produced. Initial studies in mouse models showed that intrathecal injection of ASO led to increased production of SMA protein, and improved strength. Subsequent human studies showed that 40% of children injected with the drug showed improvement of motor milestones. Additional clinical trials, though uncontrolled, continued to show a positive response. FDA then assigned it a fast track designation, priority review and orphan drug status.

Dosage recommendation is 12 mg intrathecally every 14 days for three doses. The fourth loading dose is given after 30 days of the 3rd dose. Maintenance doses are continued every 4 months. The drug is being marketed by Biogen, and the cost per dose will amount to \$ 125,000.

ASO, which modify mRNA transcription, are being used for a range of diseases, including HCV, HIV, Ebola and CMV. An ASO targeting the mRNA of GATA3 (a transcription factor that promotes Th2 responses) is being used for severe asthma. The antisense ODN mipomersen (Kynamro), which targets the mRNA of Apolipoprotein B100, received regulatory approval for use in humans with familial hypercholesterolemia. (www.fda.gov 23 December 2016)

YOUTH SUICIDES IN INDIA

Youth suicides have reached crisis levels in India. In the 1990's when Australia faced a similar situation, a concerted effort by the government saw a remarkable decline in suicide rates in young people. The December 2016 issue of the Economic and Political Weekly carries an erudite discussion of problem in India with comparisons from Australia. There appears to be little public awareness or concerted health policy to tackle this issue in India.

In Australia, between 1900 and 1990, teenage girl suicides remained between 5-10 per lakh population. In young males, from a low of 5.3 at the depths of World War II in 1943, rates

rose steadily, decade by decade. By the early 1980's, the rate was almost 23 per lakh, and by end of the decade it had reached over 33 per lakh.

It was finally labeled a 'crisis situation', and the Australian government initiated a series of reports, which culminated in the formulation of a national strategy for suicide prevention. After the National Youth Suicide Prevention Strategy, suicide rates in Australia plunged dramatically to an average of 11.9 per lakh in 15-19 year-olds and 18.4 per lakh for young adult males in the age group of 20-24 years.

Youth suicides are preventable. About 80% of teenagers contemplating suicide communicate their intention to a friend or a family member. And only one in 40 attempts results in death. A significant number never make a second attempt, and thus suicide prevention programs can be very effective.

In broad terms, the youth and young adult suicide rates in India were relatively constant at around 15 per lakh since 1967. However, the estimated all-India suicide rate in 2010 for males aged 15–29 was 25.5 per lakh, and for females it was 24.9 per lakh. Indeed, if we bear in mind the '15 per lakh equals crisis' rule of thumb, the young male suicide rates in 17 of the Indian states and territories are near or well above that rate. Strangely, Puducherry has the highest young male suicide rate in the world (82.7), far higher than the leading country Lithuania (44.9). We all need to wake up, take notice, and act. (*Economic & Political Weekly* 24 December 2016).

HEALTHCARE AUDIT IN RURAL MADHYA PRADESH

An audit of healthcare providers in rural Madhya Pradesh (MP) by economists has revealed interesting data. In a study, highly trained fake patients (called standardized patients) were coached to present symptoms like normal patients for three diseases – angina, asthma and dysentery. They made 1100 unannounced visits to public and private health facilities in rural MP. Seventy percent of private health providers, to whom these patients went, had no formal training, and would be classified as quacks as per norms of the Medical Council of India. The average time spent per patient was 2.4 minutes by public health providers, and 3.7 minutes by private providers. A diagnosis was provided by 26% and 43% of the public and providers, respectively; and it was 'correct' in 15% and 13.5%, respectively. The per patient cost of the public health care system was Rs 240, billed not to the patient but to the exchequer. The per patient consultation fee was Rs 51 in the private sector. The study concludes that most private providers "exerted significantly higher effort than public providers" and "recommend correct treatments equally often." This study provides valuable insights into what is the quality of health care available at the grass root level in India. (*The Hindu* 11 December 2016).

GOURI RAO PASSI
gouripassi@hotmail.com